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# Oxonitriles: Cyclizations in Total Synthesis

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# Oxonitriles: Cyclizations in Total Synthesis

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By
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**Acknowledgments**

- I dedicate this body of work to the two most important women in my life – my mother, Meena Iyer and my wife, Sejal Iyer; My mother for inculcating in me perseverance and a thirst for knowledge and my wife for her unwavering support through the challenges of graduate school.

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## Abstract

Oxonitriles are versatile synthetic intermediates. The thesis provides a survey of the synthesis and reactions of cyclic oxonitriles followed by an approach to Kuehneromycin A that features oxonitrile chemistry.

The discussion presents a synthetic route to the sesquiterpenoid, Kuehneromycin A, using oxonitrile-based methodology. A key feature is a new oxidative cyclization reaction that has been developed as a method for assembling functionalized *trans*-decalins. The mechanism of this reaction is presented to explain the excellent stereoselectivity. Similarly, a mechanistic analysis of a novel isomerization of quarternary centers is presented in detail.

## List of Abbreviations

| | | |
|---|---|---|
| Ac | - | acetate |
| br | - | broad |
| Bu | - | butyl |
| BuLi | - | butyllithium |
| $^{13}$C NMR | - | carbon nuclear magnetic resonance |
| d | - | doublet |
| dd | - | doublet of doublets |
| DABCO | - | 1,4-Diazabicyclo[2.2.2]octane |
| DBU | - | 1,8-Diazabicyclo[5.4.0]undec-7-ene (1,5-5) DBU |
| DMF | - | *N,N*-dimethylformamide |
| DMSO | - | dimethylsulfoxide |
| equiv | - | equivalent |
| Et | - | ethyl |
| GC-MS | - | gas chromatography-mass spectrometry |
| h | - | hour(s) |
| $^{1}$H NMR | - | proton nuclear magnetic resonance |
| $H_2SO_4$ | - | sulfuric acid |
| *i* | - | iso |
| IR | - | infrared |
| LDA | - | lithium diisopropylamine |
| m | - | multiplet |
| Me | - | methyl |
| min | - | minutes |
| MOM | - | methoxy methyl |
| Ms | - | mesylate |
| Ph | - | phenyl |
| q | - | quartet |
| R | - | alkyl, aryl, or hydrogen |

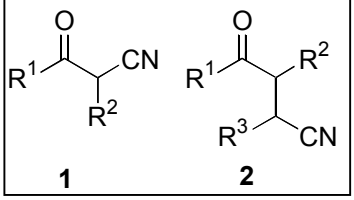
| | | |
|---|---|---|
| RAMP | - | (R)-(−)-1-Amino-2-(methoxymethyl)pyrrolidine |
| s | - | singlet |
| SAMP | - | (S)-(−)-1-Amino-2-(methoxymethyl)pyrrolidine |
| t | - | triplet |
| *t* | - | tertiary |
| Tf | - | triflate |
| TFA | - | triflouroacetic acid |
| THF | - | tetrahydrofuran |
| TMS | - | trimethylsilyl |

## Introduction

### Survey of Cyclic Oxonitriles

Oxonitriles have long occupied a distinctive niche in organic synthesis. Historically, the high acidity of β-oxonitriles allowed the facile deprotonation and alkylation in a wide variety of transformations typical of malonate-type nucleophiles. As synthetic technology advanced, ketonitriles continued to be as ideal for Robinson annulations[1] as well as for several new applications that have emerged since the last review almost 20 years ago.[2]

**Figure 1**

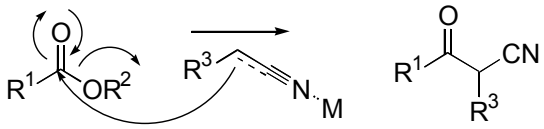



Oxonitriles are partitioned into two main classes: β-oxonitriles **1,** where the groups are separated by one carbon and γ-oxonitriles **2**, where the nitrile group is two carbons removed from the carbonyl group (Figure 1). The unique reactivity of oxonitriles stems from the juxtaposition of two strongly electon withdrawing groups in close proximity that interact to exhibit synergistic reactivity. In general the reactions of saturated oxonitriles reflect the high acidity of the proton(s) adjacent to the carbonyl group, whereas the unsaturated analogs are highly polarized electrophiles, ideally suited for participation in Michael and cycloaddition reactions. The chemistry of β-oxonitriles is significantly less diverse, and tends to be dominated by their formation through $Et_2AlCN$ addition to enones followed by ketone functional group manipulation. Collectively, these features have endeared oxonitriles for a variety of synthetic ventures, particularly since most reactions install nitrile and ketone functionalities ideally positioned for further elaboration.

## A. β-Oxonitrile Syntheses

### 1. Nitrile Claisen Condensations

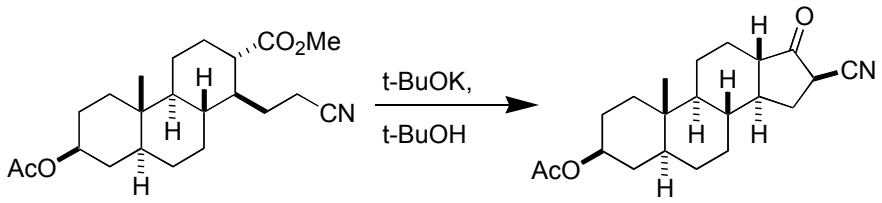
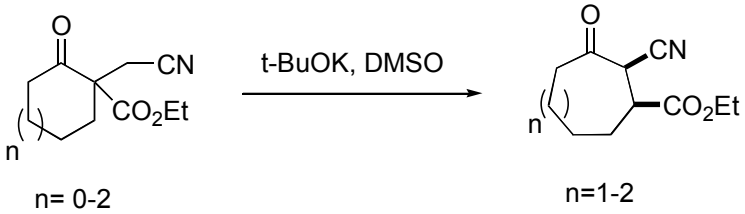
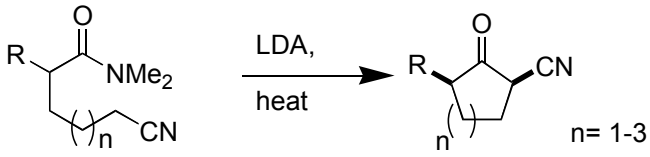
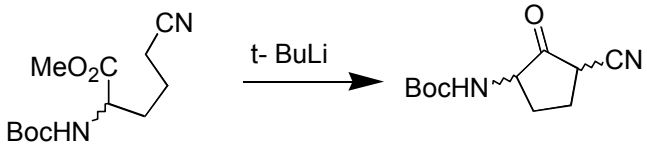
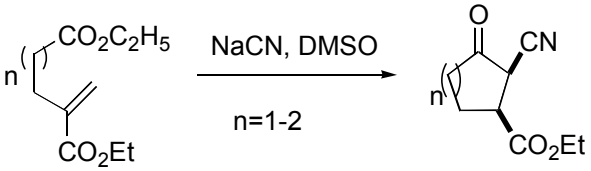
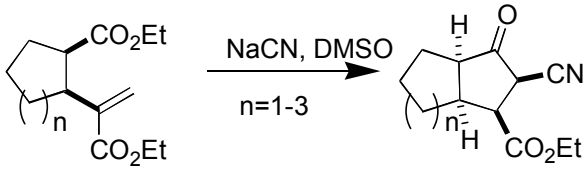
Scheme 1

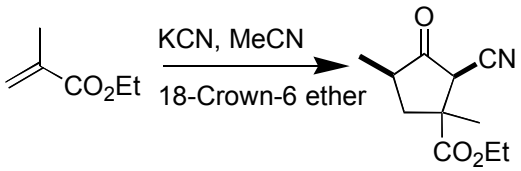
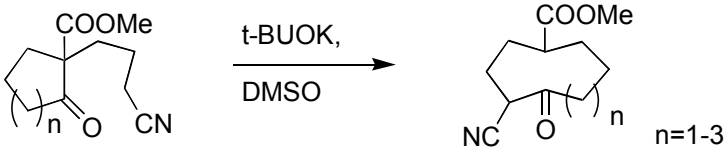
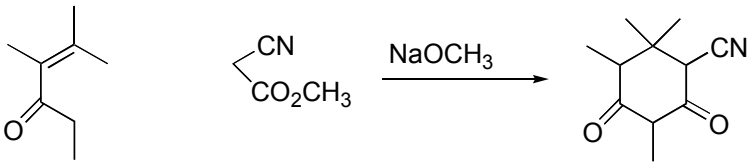
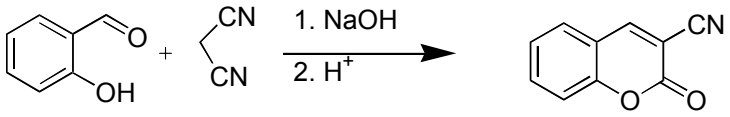



β-Oxonitriles are most commonly prepared by condensing an excess of a metallated nitrile with an ester (Scheme 1, Table 1). Addition of the metallated nitrile generates an intermediate that rapidly eliminates alkoxide to generate the acidic oxonitrile. Consequently, an additional equivalent of base, typically in the form of excess metallated nitrile, is essential since the β-oxonitrile is more easily deprotonated by the metallated nitrile than addition to the carbonyl group of the reactant ester.

Despite the use of excess base, chiral esters with potentially epimerizable stereocenters are not stereochemically compromised (Table 1, entry 3). The availability of esters renders these as the most common carbonyl acceptors though a variety of activated esters and amides react with comparable efficiency. Intermolecular and intramolecular reactions are equally effective since, although esters are more easily deprotonated than nitriles,[3] rapid proton transfer[4] ensures access to the metallated nitrile that is an excellent nucleophile that rapidly reacts with the carbonyl acceptor. In contrast, the nitrile is a poor electrophile[5, 6] that is not readily attacked by ester and amide enolates. The preference for intramolecular cyclization of a metallated nitrile with a pendant ester is the basis for the conjugate addition of cyanide to substituted acrylates (Table 1, entries 5-7). Conjugate cyanation generates an ester enolate that equilibriates to a metallated nitrile, probably via intermolecular proton transfers, followed by acylation with the pendant ester moiety.

**Table I: Cyclic β-oxonitriles Via Metallated Nitrile-Carbonyl Condensations**

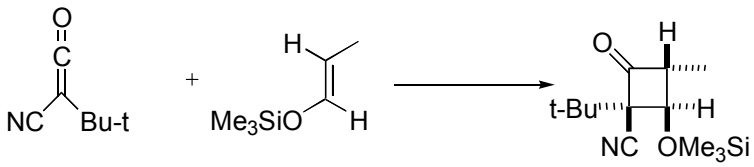
| Entry | Reaction | Yield (%) |
|---|---|---|
| 1. |  | 50[14] |
| 2. |  | 37-57[15] |
| 3. |  | 75-89[13] |
| 4. |  | 50[98] |
| 5. |  | 73-84[30] |
| 6. |  | 60-71[31] |

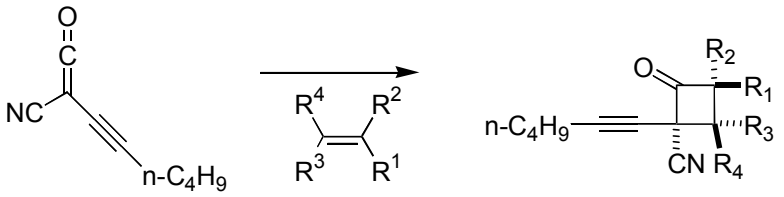
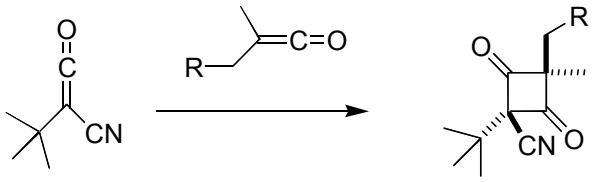
| | | |
|---|---|---|
| 7. |  | 62[99] |
| 8. |  | 57-63[16] |
| 9. |  | 68[9] |
| 10. |  | 75-95[12] |

**2. Cycloaddition**

Nitrile-substituted ketenes react with electron rich alkenes in [2+2] cycloadditions (Table II). Activation of ketenes by the electron withdrawing nitrile group provides a facile route to the nitrile-substituted cyclobutenones.

**Table II: β-Oxocyclobutanecarbonitrile Synthesis by Cyanoketene Cycloaddition**

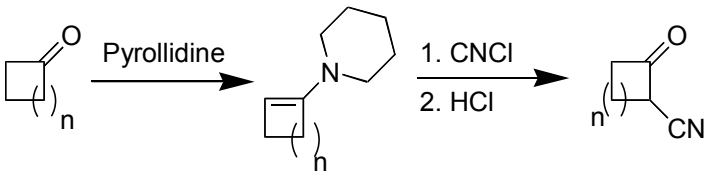
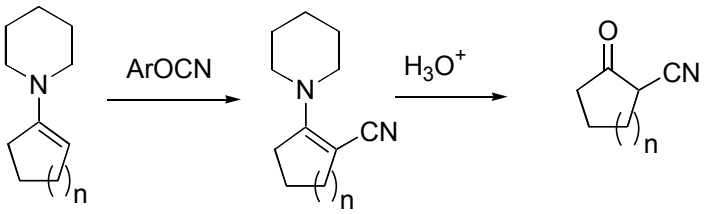
| Entry | Reaction | Yield (%) |
|---|---|---|
| 1. |  | -[17] |

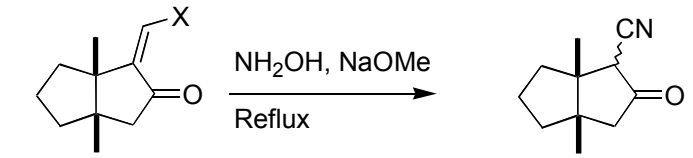
| | | | |
|---|---|---|---|
| 2. |  | | 44-75[19] |
| 3. |  | | 38-44[20] |

### 3. Miscellaneous Syntheses of Cyclic β-oxonitriles

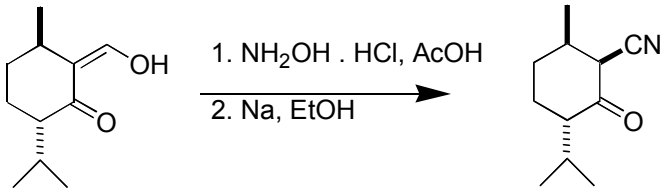
Cyanation of ketone enolates, and their synthetic equivalents, provides a robust synthesis of β-oxonitriles, ideally suited to cyclic oxonitriles. Historically, the source of electrophilic cyanide was gaseous cyanogen chloride. The introduction of more easily manipulated arylcyanates, phenyl cyanate in particular,[111] significantly facilitated cyanation reactions (Table III, entries 1-2).[119]

**Table III: Miscellaneous Syntheses of Cyclic β-Oxonitriles**

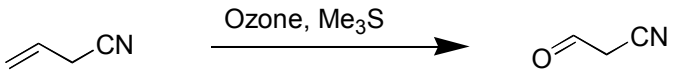
| Entry | Reaction | Yield (%) |
|---|---|---|
| 1. |  | 46-77[27] |
| 2. |  | 25-36[28,29] |

3 

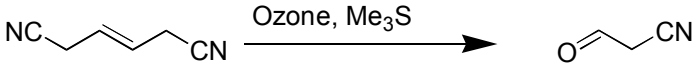
X= OH; X= $SC_4H_9$ 89[25]

4 

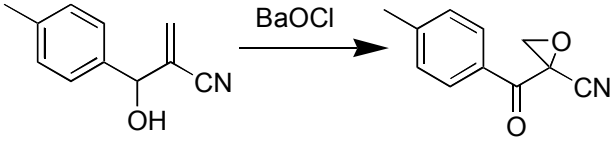
-[26]

5 

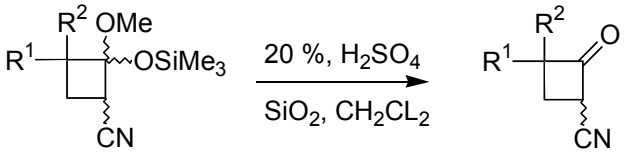
71[33]

6 

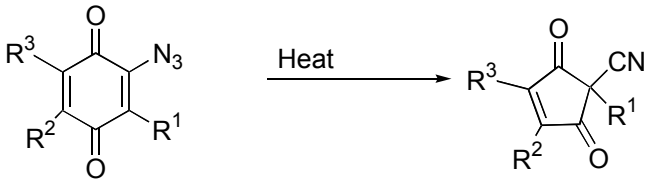
71[33]

7. 

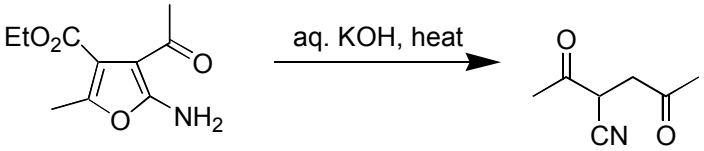
66-98[34]

8. 

82-90[36]

9 

55-60[21, 22]

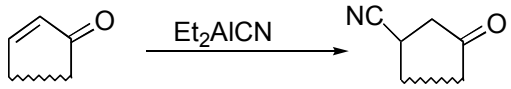
10 

35[24]

Numerous methods exist for the dehydration of oximes to nitriles which have been employed in synthesizing cyclic nitriles (Table III, entries 3-4). The parent oxonitrile "cyanoacetaldehyde" is particularly labile but readily prepared by ozonolysis and then used in situ (Table III, entries 5-6).

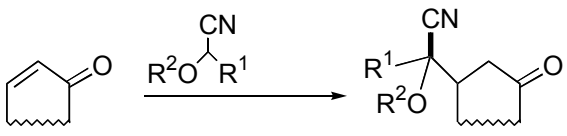
**B. γ-Oxonitrile Syntheses**

γ-Oxonitriles are synthesized by two main routes: conjugate addition of cyanide to enones and through the stepwise conjugate addition-hydrolysis of metallated cyanohydrins to alkenenitriles.[121] The conjugate addition of cyanide that usually employs $Et_2AlCN$ (prepared from $Et_3Al$ and HCN and is often referred to as the Nagata reagent), is a "classic" that has been extensively reviewed (Eq 1).[155]



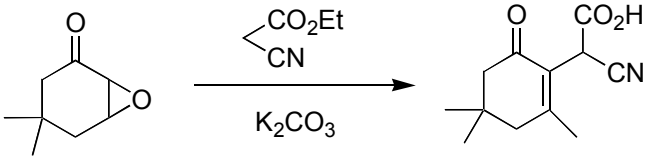
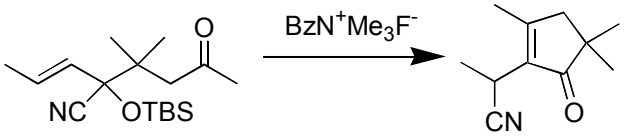
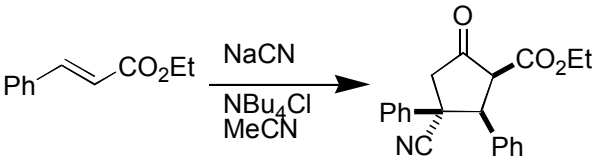
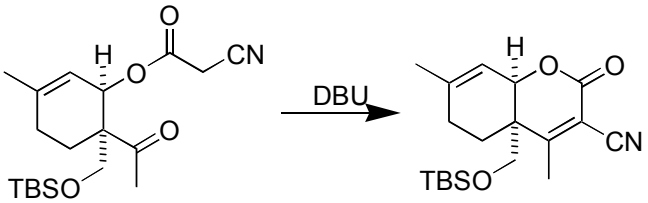

**Eq 1**

The conjugate addition of metallated cyanohydrins and related nucleophiles represents a well-established acyl anion route to oxonitriles (Eq 2).[121] The method is restricted to cyanohydrins derived from aromatic aldehydes, although this substrate requirement complements the types of substrates generally accessed by the Nagata reagent. Conjugate additions with acyl cyanohydrins generate oxonitriles that are usually hydrolysed to 1,4-diketones.




**Eq 2**

**Table V**

| Entry | Reaction | Yield (%) |
|---|---|---|
| 1. |  | 51-90[36] |
| 2. |  | 77[37] |
| 3. |  | 56[99] |
| 4. |  | 100[92] |

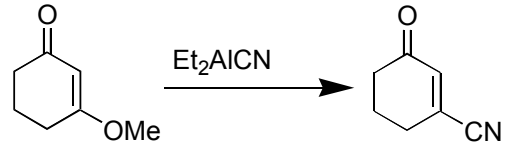
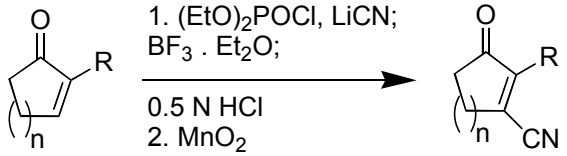
## C. Unsaturated Oxonitrile Syntheses

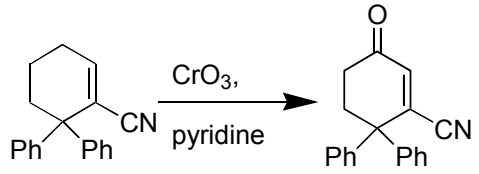
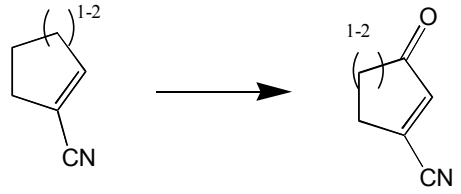
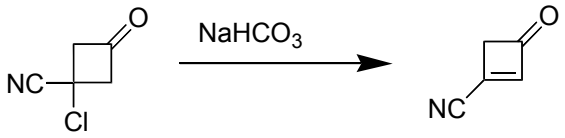
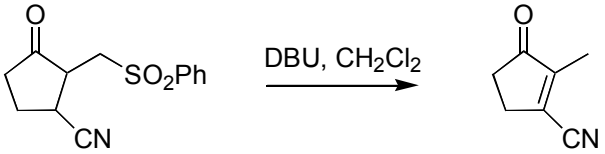
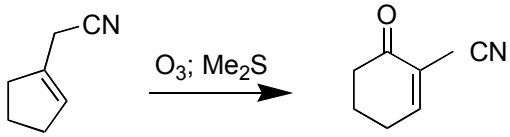
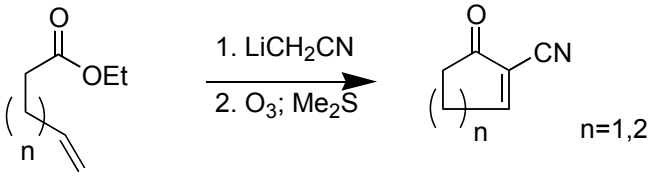
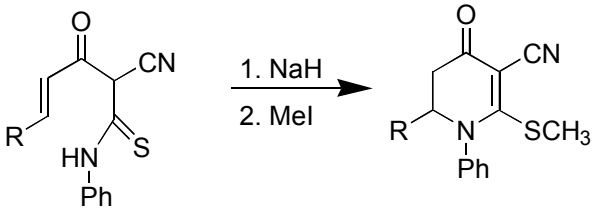
Oxoalkenenitriles are typically generated by an elimination of substituted oxonitriles or by oxidation of alkenenitriles. Conjugate cyanation followed by ejection of methoxide has historically been the most common method of generating cyclic γ-oxoalkenenitriles (Table VI, entry 1). An alternative is the [2,3] rearrangement of phosphorylated cyanohydrins generated with $(EtO)_2POCN$ , LiCN and an enone which, after hydrolysis and oxidation, affords a γ-oxoalkenenitrile (Table VI, Entry 2). A more direct, though less common alternative, is the allylic oxidation of a cyclohexenecarbonitrile (Table VI,

Entry 3). The yield is excellent with cyclohexenecarbonitriles but falls dramatically with cyclopentenecarbonitriles. γ-Oxoalkenenitriles with pendant leaving groups undergo elimination, preferentially generating the more conjugated oxonitrile (Table VI, entries 5-6).

The synthesis of alkylidene β-oxonitriles is considerably more challenging because the products are excellent electrophiles. Sulfoxide and selenoxide eliminations are sufficiently mild for this purpose, providing the facile conversion of cyclic β-oxonitriles to their unsaturated counterparts (Table V, entries 6-7). An efficient alternative is the ozonolysis of an unsaturated nitrile, followed by an intramolecular aldol reaction and in-situ dehydration to give the unsaturated oxonitriles in one synthetic operation (Table V, entries 8-9).

**Table VI: Unsaturated Oxonitrile Syntheses**

| Entry | Reaction | Yield (%) |
|---|---|---|
| 1. |   | -[41] |
| 2. |   | -[42] |

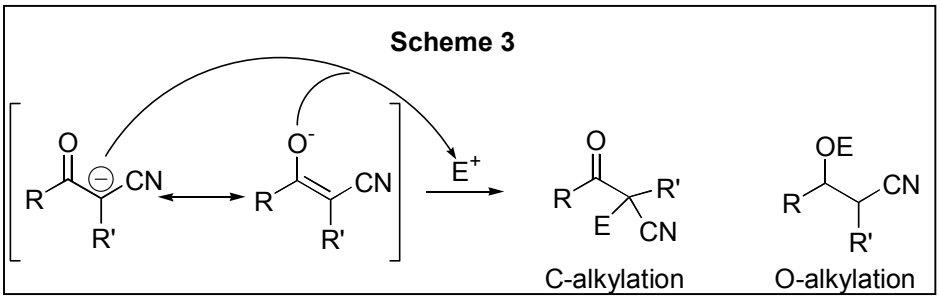
| | | |
|---|---|---|
| 3. |  | 86[43] |
| 4. |  | 25-65[110] |
| 5. |  | 90[45] |
| 6. |  | 51[46] |
| 7. |  | -[100] |
| 8. |  | 95[47] |
| 9. |  | 53-91[48] |
| 10. |  | 90-93[72] |

**D. Reactions of Oxonitriles**

ß-Oxonitriles are usually generated as synthetic intermediates since they neither occur naturally [46] and only seldom in medicinal compounds.[108] Rather, ß-oxonitriles are valuable precursors to a variety of chemically and biological targets.

**1. Alkylation of β-Oxonitriles**

Historically, the high acidity (pKa =9-11) of enolizable β-oxonitriles permitted facile deprotonation and alkylation with alkoxide bases (Scheme 3)[122] The ambident

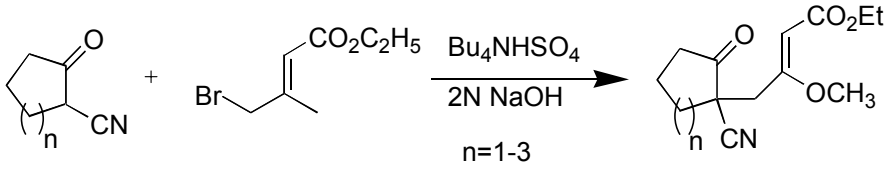
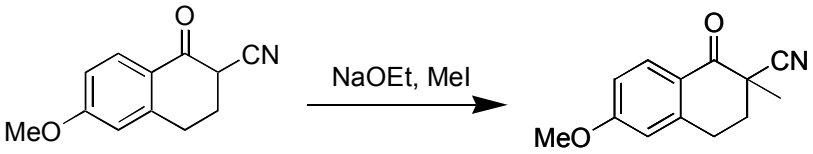
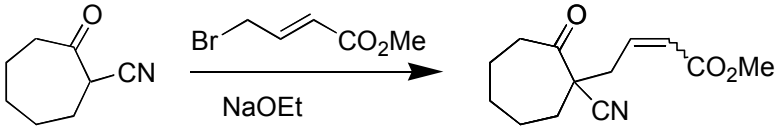
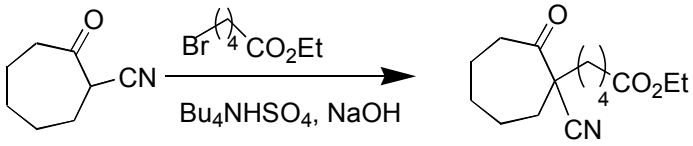
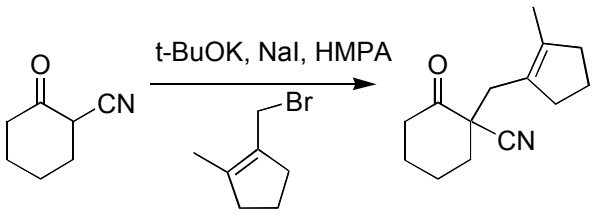


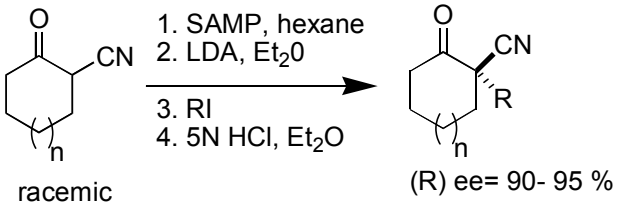

nucleophilicity of the enolates permits O- and C-alkylation with the preference paralleling the reactivity exhibited by enolates. Soft electrophiles react on carbon (Table VII) whereas harder electrophiles alkylate on oxygen (Table VIII).

The low pKa of β-oxonitriles permits the use of a variety of weak bases for the deprotonation, although strong bases such as NaH, NaOH, LDA and t-BuOK have also been used. C-alkylation of endocyclic β-oxonitriles necessarily installs a stereogenic quaternary center often resulting in a mixture of diastereomers. Excellent stereoselectivity is observed in alkylations of the SAMP derived hydrazones (Table VII, entry 6).

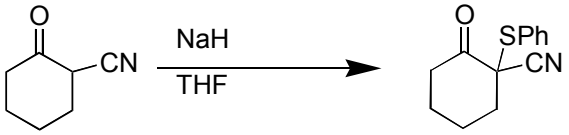
Cyclic β-oxonitriles are excellent partners for Robinson annulation. The initial conjugate adduct is derived by alkylation from the axial direction (Table VII, entry 10) and, under equilibrating conditions, generates an enolate for further cyclization onto the carbonyl compound. The 1,6-addition to the vinyl-butenolide is anticipated for the soft metallated oxonitrile, allowing for a concise route to the Endomere skeleton.

**Table VII: C-Alkylation of ß-Oxonitriles**

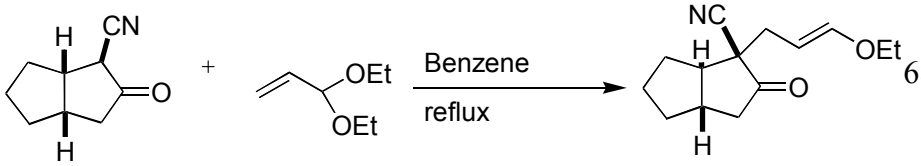
| Entry | Reaction | Yield (%) |
|---|---|---|
| 1. |   | 80-82[48] |
| 2. |   | -[49] |
| 3. |   | 87[49] |
| 4. |   | 62[49] |
| 5. |   | 87[51] |

6. 

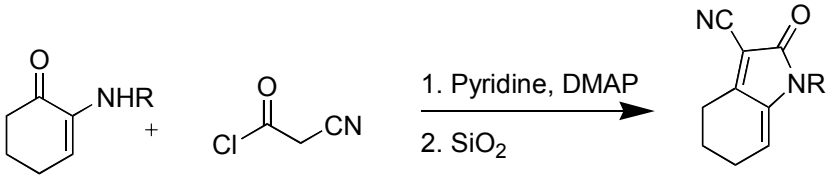
-[53]

7. 

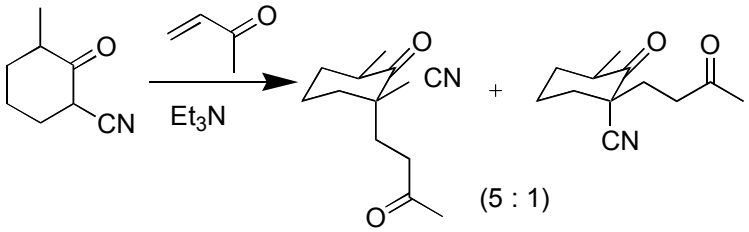
79[54]

8. 

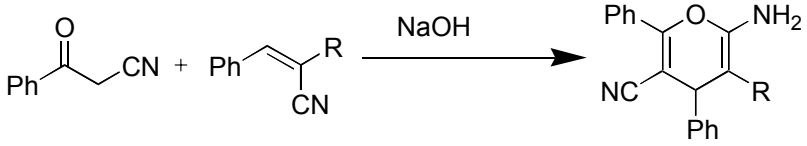
68-71[61]

9. 

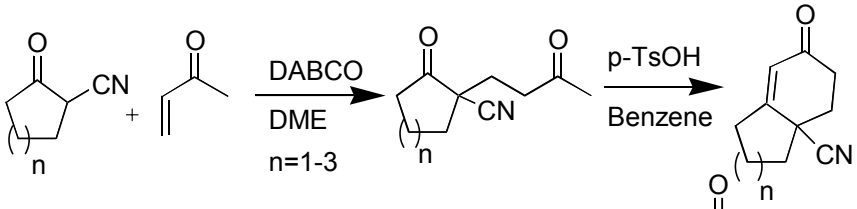
16-32[62]

10. 

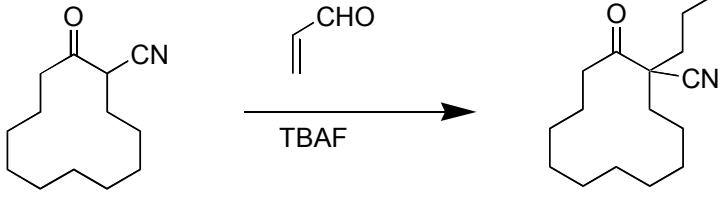
-[101]

11. 

42-90[75]

12. 

74-99

13. 

39-72[59]

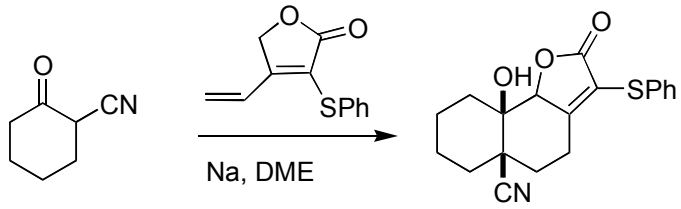
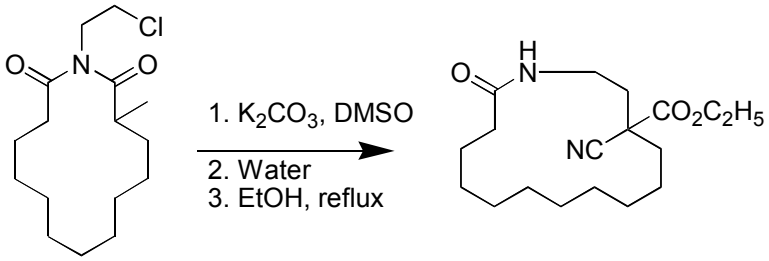
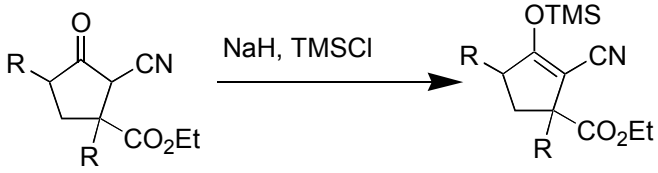
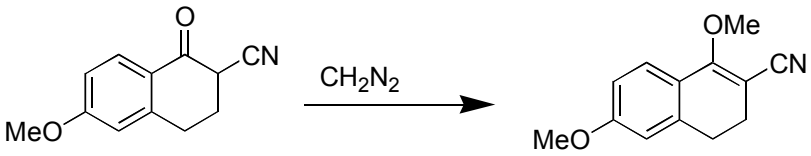
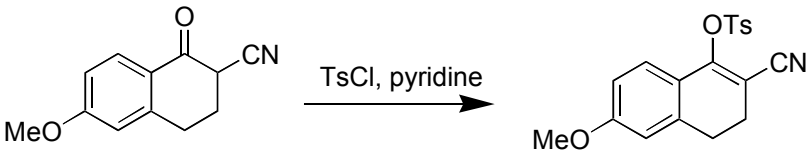
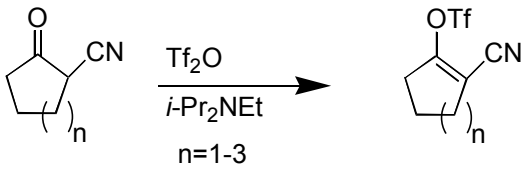
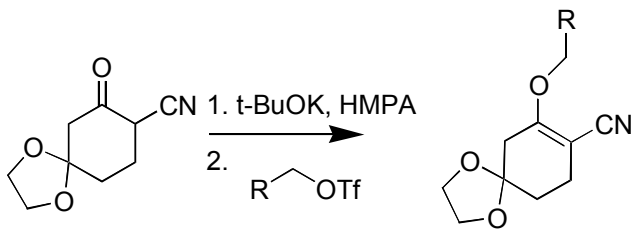
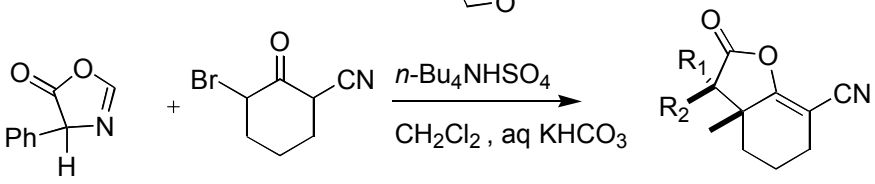
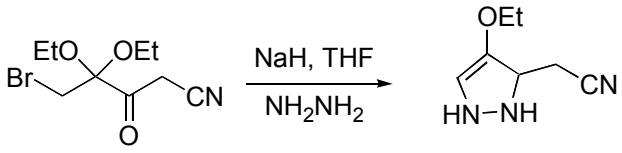
| | | |
|---|---|---|
| 14. |   | $53^{58}$ |
| 15. |   | $63^{86}$ |

**Table VIII. O-Alkylation of β-Ketonitriles**

| Entry | Reaction | Yield (%) |
|---|---|---|
| 1. |   | $79^{63}$ |
| 2. |   | $95^{64}$ |
| 3. |   | $50^{64}$ |
| 4. |   | $75\text{-}77^{65}$ |

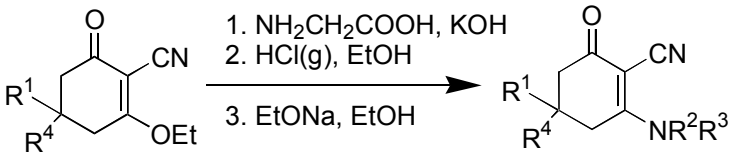
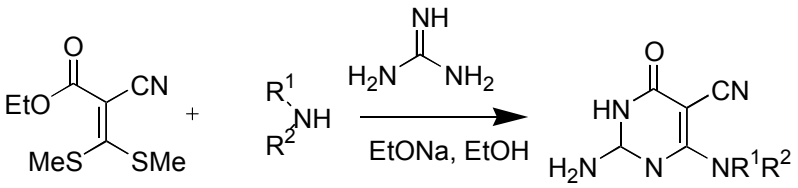
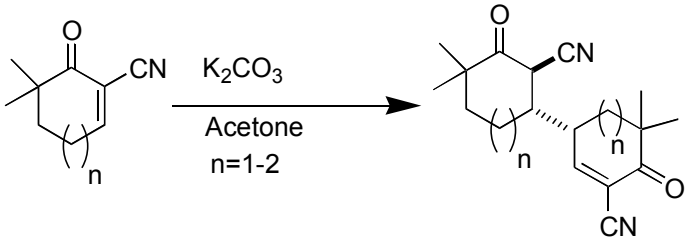
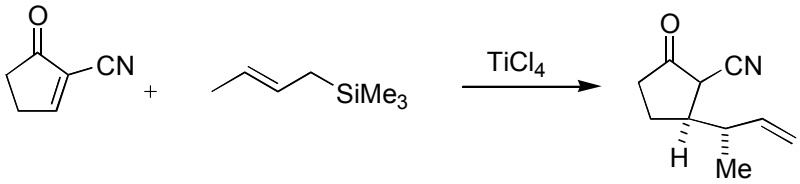
| | | |
|---|---|---|
| 5. |  | 68[66] |
| 6. |  | 50-60[68] |
| 7. |  | 56[69] |

## 2. Conjugate Addition to Unsaturated ß-Oxonitriles

Unsaturated ß-oxonitriles are excellent Michael acceptors as attested by the reactivity of superglue, α-cyanoacrylate! The highly polarized electrophiles react conjugately with a diverse arrary of sulfur, nitrogen and carbon electrophiles, with Grignard reagents reacting exclusively by 1,4-addition with no detectable addition to the carbonyl group (Table IX). Conjugate addition to oxoalkenenitriles containing β-alkoxy, β-amino, or β-alkylthio groups trigger sequential Michael addition-eliminations (Table IX, entries 1-2). In the presence of base, self-condensation can occur, although this appears to be less facile than the addition of nucleophiles.

**Table IX. Conjugate Additions to Unsaturated β-Oxonitriles**

| Entry | Reaction | Yield (%) |
|---|---|---|

| | | |
|---|---|---|
| 1. |  | 80[70] |
| 2. |  | 47-57[74] |
| 3. |  | 35[71] |
| 4. |  | -[73] |

## 3. β - Oxonitrile Ring Expansion

An excellent series of ring expansions have been developed using β-oxonitrile alkylation followed by ring closure-ring opening. Mechanistically, alkylation of the β-oxonitrile with an electrophile bearing a pendant nucleophile X permits subsequent internal attack on the ketone followed by fragmentation of the β-alkoxy nitrile (Scheme 4). Protonation of the resulting nitrile anion renders the fragmentation irreversible. In an extension of the method, initial alkylation with isocyanates or diimides leads to annulation of a 9-membered intermediate whose fragmentation is further favored by relief of ring strain (Table X, Entry 4). Overall the sequence represents an n+2 ring enlargement from a carbocyclic ring to a heterocyclic ring.

**Scheme 4**

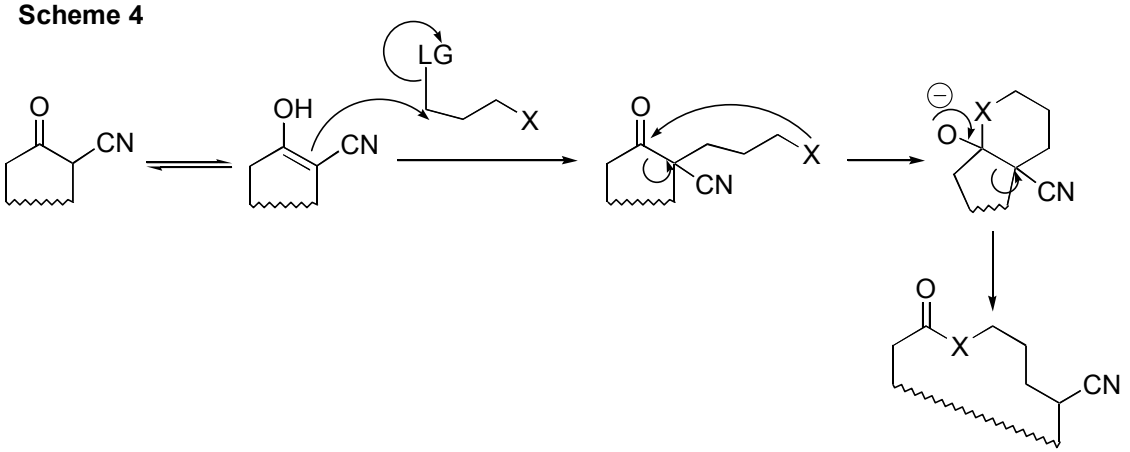
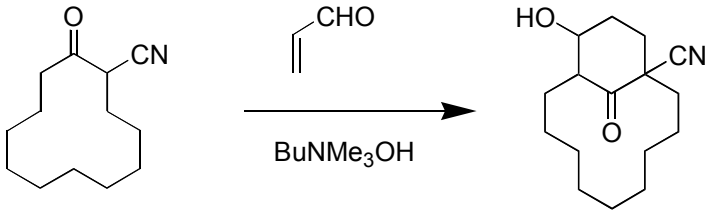
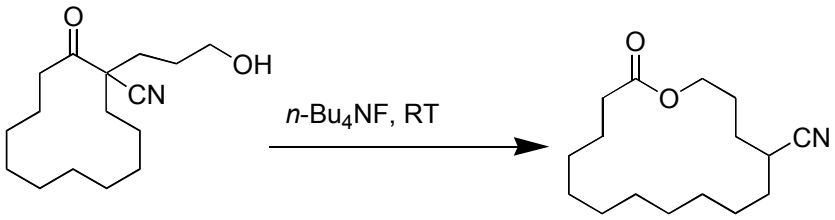
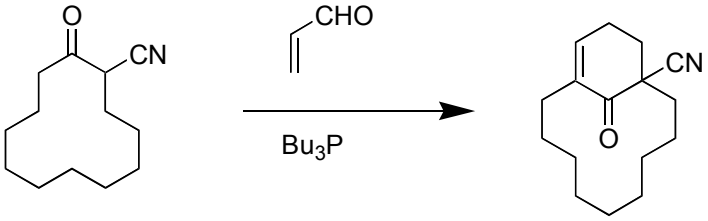
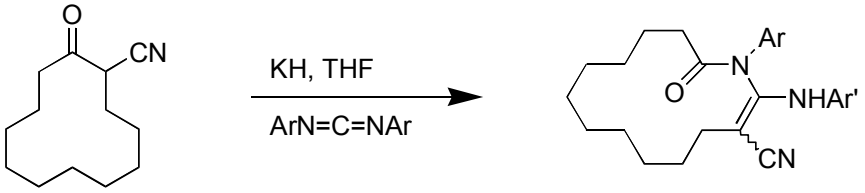



**Table X: Ring Expansions of ß-Oxonitriles**

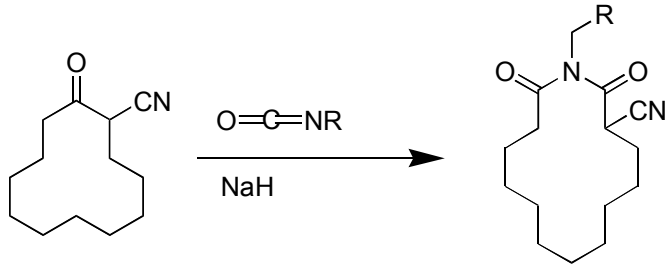
| Entry | Reaction | Yield (%) |
|---|---|---|
| 1. |   | 39-72[59] |
| 2. |   | -[103] |

3. 

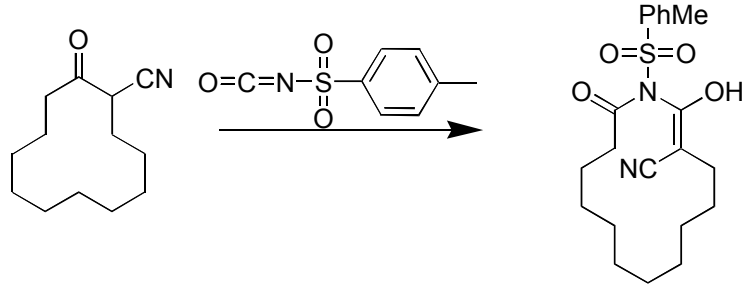
39-72[85]

4. 

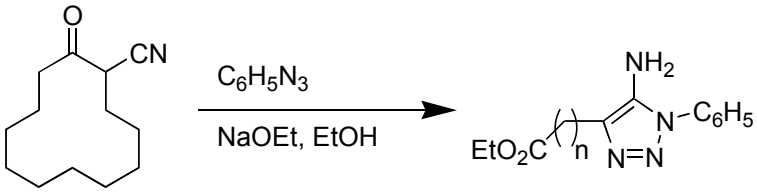
-[87]

5. 

72-75[86]

6. 

95[90]

7. 

60[89]

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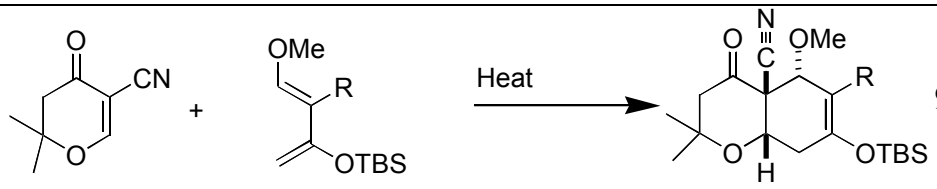
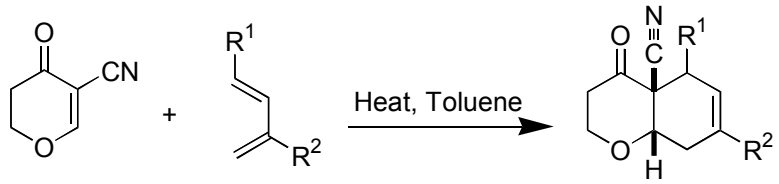
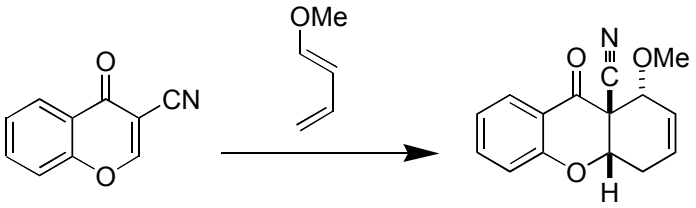
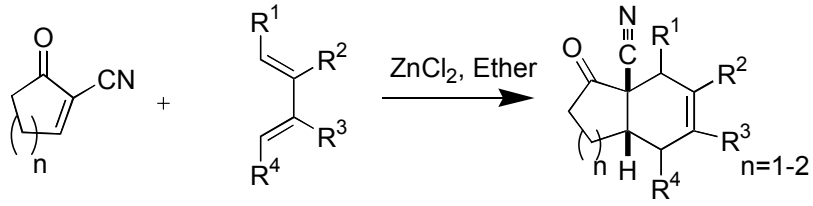
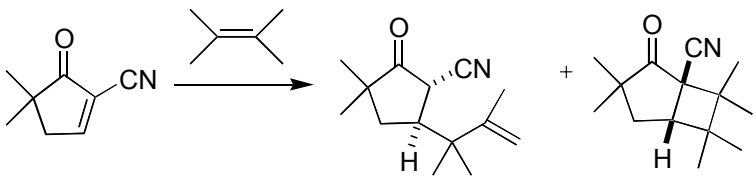
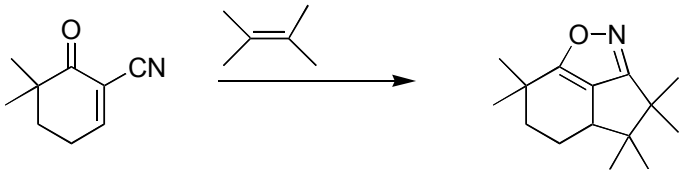
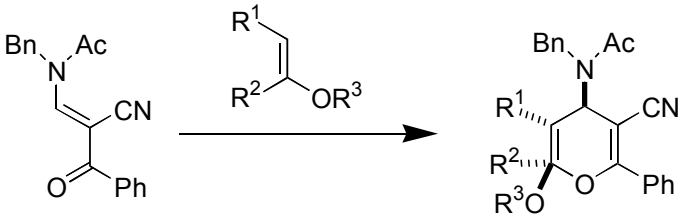
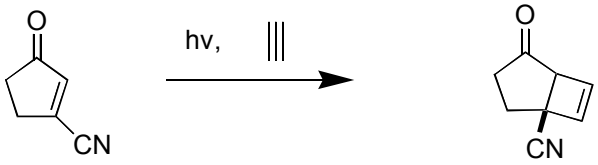
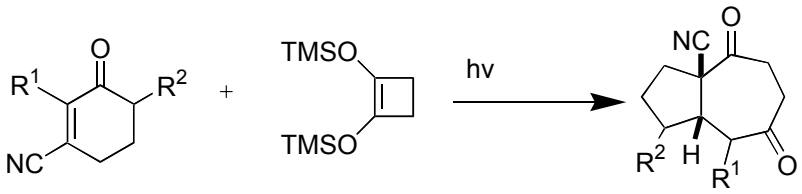
## 4. Cycloadditions of Oxoalkenenitriles

The high polarization of unsaturated oxonitriles predisposes ß and γ- oxoalkenenitriles toward cycloaddition reactions. The extremely electron deficient β-oxoalkenenitriles are highly activated dienophiles, reacting even with unactivated dienes such as butadiene

(Table XI, Entry 4). Unlike the usual high temperature required in many Diels-Alders reactions, these reactions take place at room temperature in the presence of $ZnCl_2$. Similarly, incorporation of an adjacent oxygen, as in the pyrans, does not significantly attenuate the reactivity efficiently providing bicyclic oxadecalins (Table XI, Entries 1-3).

**Table XI. Cycloaddition Reaction of Unsaturated γ-Oxonitriles**

| Entry | Reaction | Yield (%) |
|---|---|---|
| 1. |  | 92-93[76] |
| 2. |  | 38-83[77] |
| 3. |  | 83[79] |
| 4. |  | 70-90[78] |
| 5. |  | -[83] |

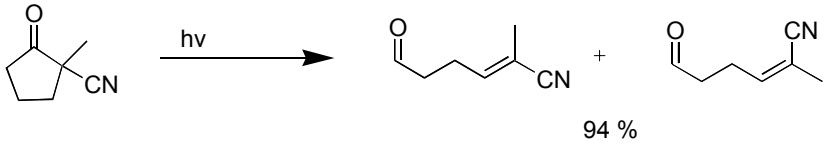
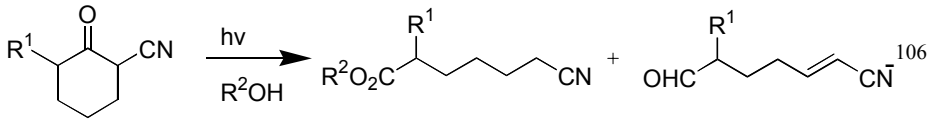
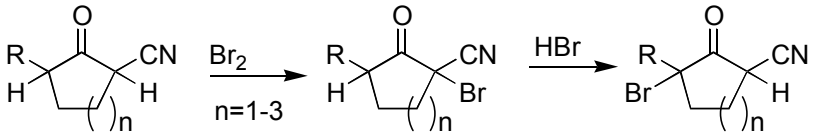
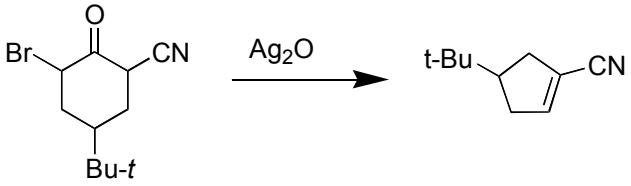
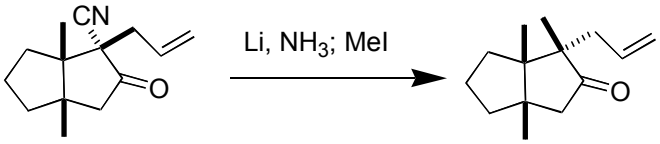
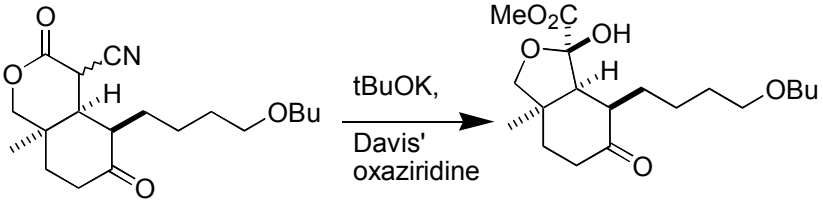
| | | |
|---|---|---|
| 6. |  | 95[83] |
| 7. |  | 57-90[81] |
| 8. |  | -[81] |
| 9. |  | 73[80] |

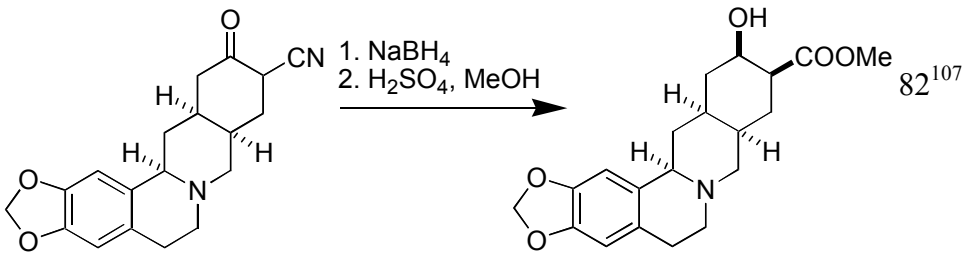
Unsaturated γ-oxonitriles, while not as highly polarized as unsaturated ß-oxonitriles, are particularly electron deficient (Table XI, Entries 8-9). The electron deficiency of the double bond lowers the LUMO to make these particularly reactive partners in photochemical cycloaddition reactions.

## 5. Miscellaneous Reactions

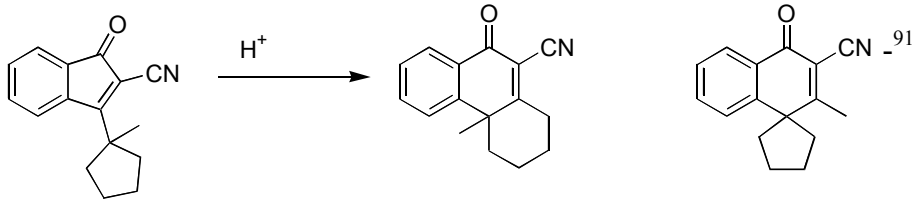
Norrish Type II cleavage of cyclic ß-oxonitriles occurs under irradiation, leading to the anticipated aldehydes (Table XII, Entries 1-2). Halogenated oxonitriles, available by bromination (Table XII, Entry 3), undergo ring contraction in the presence of silver oxide (Table XII, Entry 3).

**Table XII**

| Entry | Reaction | Yield (%) |
|---|---|---|
| 1. |   | -104,105 |
| 2. |   | 106 |
| 3. |   | -[57] |
| 4. |   | 37[106] |
| 5. |   | 58[95] |
| 6. |   | 81[96] |

7. 

82[107]

8. 

-[91]

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Under reducing conditions, ß-oxonitriles can eject the nitrile group, that functions as a pseudohalide,[156] to regiospecifically generate an active enolate for alkylation (Table XII). Enolate oxidation and rearrangement of the cyanohydrin ejects cyanide in a formal ring construction (Table XII, entry 6).

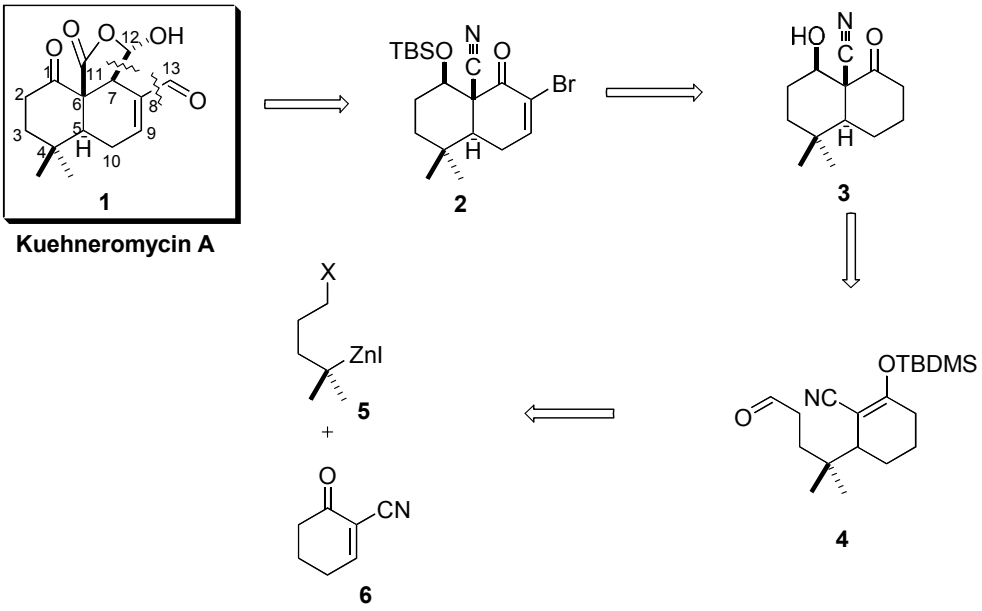
## 2.0 Discussion

### 2.1 Background

Acquired Immuno Deficiency Syndrome (AIDS) has reached epidemic proportions.[117] The causative virus, human immunodeficiency virus (HIV), rapidly mutates requiring multiple drugs treatments to contain the virus before resistance thwarts available treatment.[117] Currently the main two treatment avenues are through protease inhibitors and nucleoside mimics that are supplemented with Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI).[117] NNRTIs interact non-competitively with an allosteric site, preventing the enzyme from opening the RNA thereby preventing replication. Several NNRTIs, such as nevirapine, delavirdine and efavirenz, have been recently approved as anti-HIV drugs by the FDA and show particular promise in combination with other drug therapies.[118-123]

The search for novel AIDS inhibitors has uncovered several structurally-novel candidates. Conceptually, new inhibitors having novel structures offer the possibility of supplementing available drug targets and extending the current range of treatments available for preventing viral replication. In the mid-1990s, a structurally novel class of sesquiterpenoids were isolated from target cultures that exhibited potent activity as NNRTIs.[122-123, 124-125] Among these sesquiterpenoids, Kuehneromycin A **(1)**, was found to be the most effective NNRTI. The key structural features imparting the efficacy are as yet undetermined, although these are likely to be the enal and lactol moieties that are common to several related Kuehneromycins isolated from the same source.

**Scheme 1. Kuehneromycin A Retrosynthesis**




The highly oxygenated core of Kuehneromycin A requires careful installation of the oxidized decalin system. In a retrosynthetic sense, disconnection of carbons 12 and 13 reveals a decalin where the two carbon units could arise from a Stille coupling[154] and a Peterson olefination (Scheme 1).[131] Decalin **3** could be derived from **4**, through a key intramolecular aldol cyclization. The impetus for the approach lies in part in the facile conjugate addition-silylation of the organozinc reagent **5** (X= Cl), to the oxonitrile 6 that is readily available in a single step by an ozonolysis cascade reaction.[128]

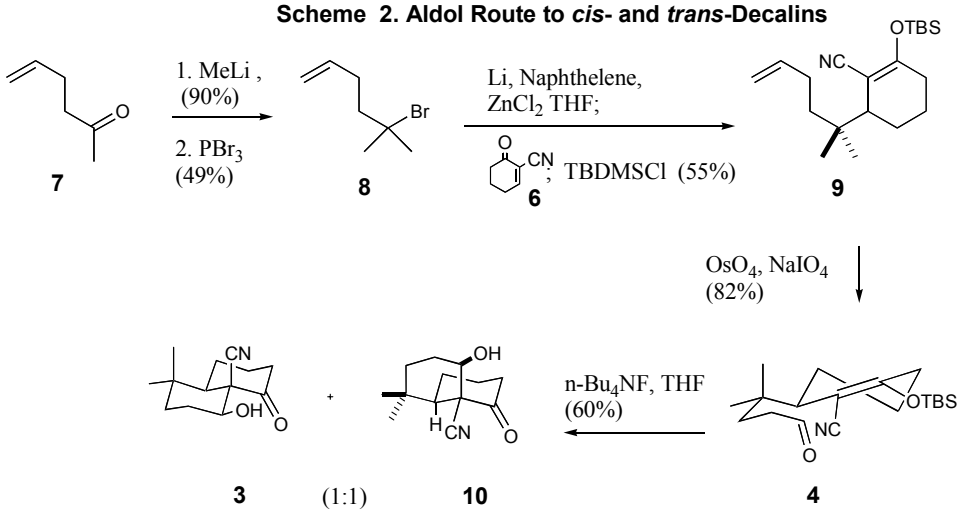
## 2.2 Aldol Route to the *trans*-Decalin

A major attraction of the aldol route is the projected 3-step construction of the decalin **3**. Methylation of commercially available 5-hexen-2-one with methyl lithium followed by bromination with phosphorus tribromide gave the tertiary bromide **8**,[126] that was converted to the corresponding organozinc reagent with Reike zinc (Scheme 2).[127] Although the organozinc reagent is less reactive than the corresponding Grignard reagent, the oxonitrile **6**[128] is an excellent Michael acceptor,[129] facilitating the conjugate addition-silylation. Unfortunately, the reaction was inconsistent, affording the conjugate adduct in yields ranging from 0-70 %. The problem appears to lie in a premature cyclization onto

the alkene to afford a cyclobutyl zinc reagent that may occur during formation of the reagent or once the organo-zinc reagent is formed since these reagents are thought to have radicaloid character. [130]

Access to the conjugate addition product **9**, although hampered by reproducibility problems, allowed the key aldol cyclization to be probed.[131] Installation of the electrophilic oxygen was easily achieved by selective oxidative cleavage of the more accessible alkene using osmium tetroxide and sodium periodate[134] to afford aldehyde **4**. Fluoride induced cleavage of the silyl ether unmasked an enolate that cyclized to a mixture of decalin stereoisomers. Based on the results obtained from X-ray crystallography and NMR analysis these were assigned as the *cis*- and *trans*-decalins **10**

**Scheme 2. Aldol Route to *cis*- and *trans*-Decalins**

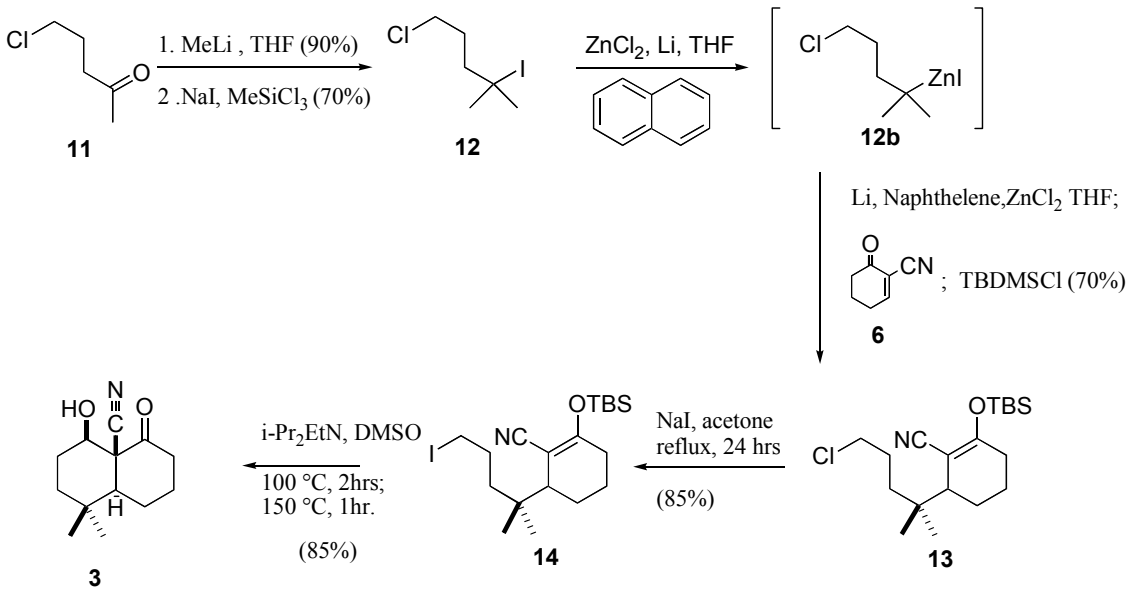



and **3**, respectively. Despite the *trans*-decalin **3** being energetically favored over the *cis*-decalin, extensive attempts to equilibriate the *cis*-decalin **10** to **3** were futile. Thus, because of these dual difficulties of irreproducible yields in the conjugate addition reaction and the cyclization, a revised approach to the *trans*-decalin **3** had to be designed.

## 2.3 Halo-Zinc Route to the *trans*-Decalin 3

Concurrent with the synthetic endeavor, a related strategy had established a route to **13,** using the organozinc reagent **12b** and oxonitrile **6** (Scheme 3).[132] The pendant chloride circumvents cyclization but provides potential functionality for introducing oxygenation at the terminal carbon. Oxidation requires prior halogen displacement that usually proceeds most efficiently with the iodide, and significantly less so with the corresponding chloride.[133] Consequently, the chloride **13** was converted to the corresponding iodide **14** using the Finkelstein protocol[134]. Halogen oxidation, although initially difficult, ultimately proved extremely rewarding in providing an exceptionally concise route to decalin **3** (Scheme 3).

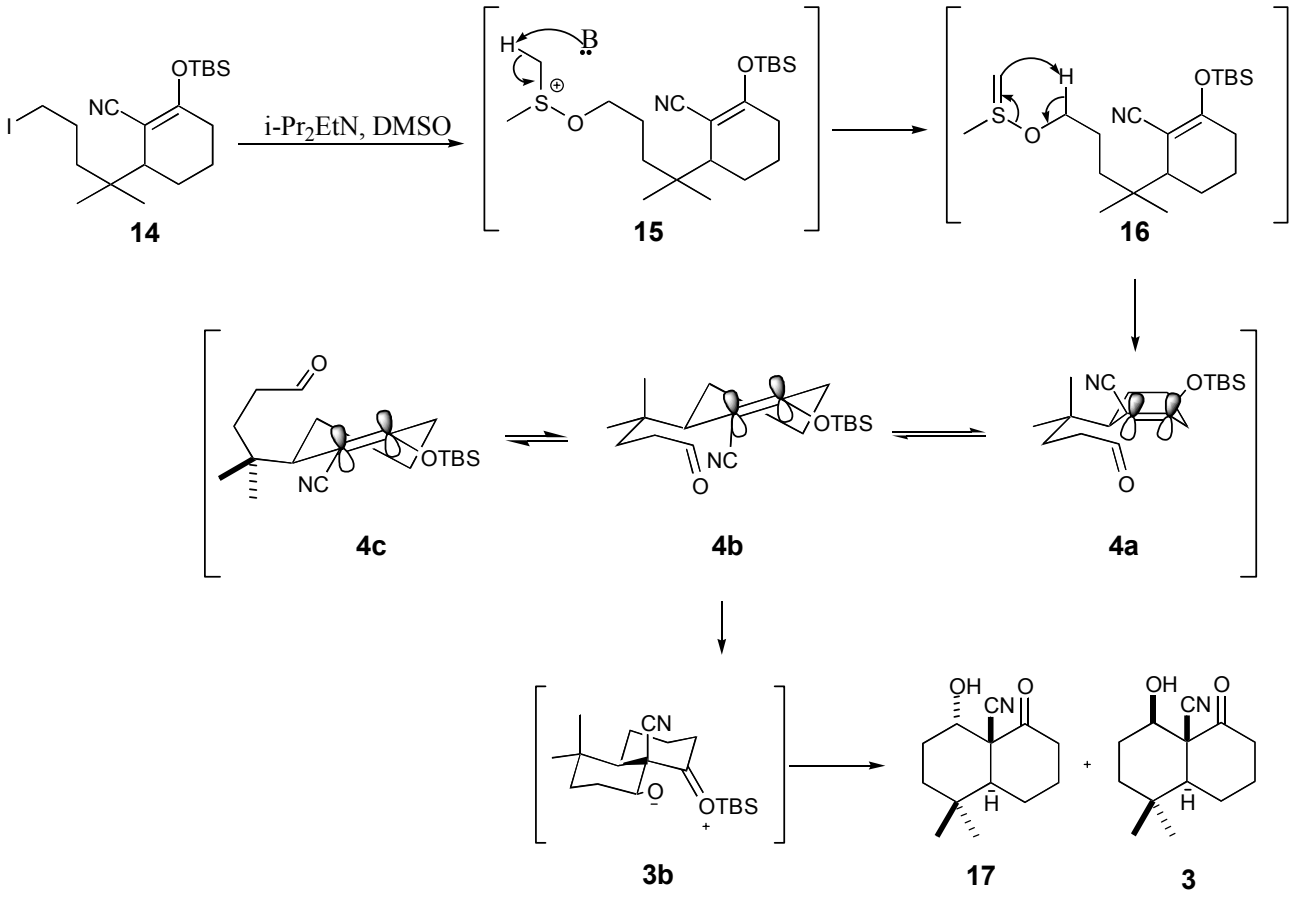
**Scheme 3. Oxidative-Aldol Route to *trans*-Decalin 3**




The dimethylsulfoxide displacement, although effective in small molecules, proved difficult to optimize causing a detailed examination of the Kornblum oxidation. Historically, the Kornblum oxidation[133] was the first DMSO-based oxidation, proceeding through an initial iodine displacement by the sulfoxide oxygen. Although this displacement requires elevated temperatures, the reaction permits the facile oxidation of **14** although several other components are also generated. An extensive screening of time and temperature revealed that the major component was the desired *trans* decalin **3**,[157] generated in 85% yield (Scheme 3).

Mechanistically the oxidative cyclization results from the combination of a Kornblum oxidation and a Mukaiyama aldol cyclization[135] (Scheme 4). Optimization studies revealed that the initial DMSO displacement requires 2 h at 100 °C leading, after deprotonation with *i*-$Pr_2NEt$ to the aldehyde **4** via the sulfonium ylide **16**. Increasing the temperature to 150 °C for 30 min after the initial two hours triggers cyclization of the enol silyl ether onto the aldehyde to generate **3**, in some instances with varying amounts of the epimeric nitrile **17**. Exclusive formation of **17** occurred by heating only briefly at 150 °C (10 min), suggesting that **17** is the kinetic decalin formed en route to **3**.

**Scheme 4. Oxidative-Aldol Cyclization Mechanism**



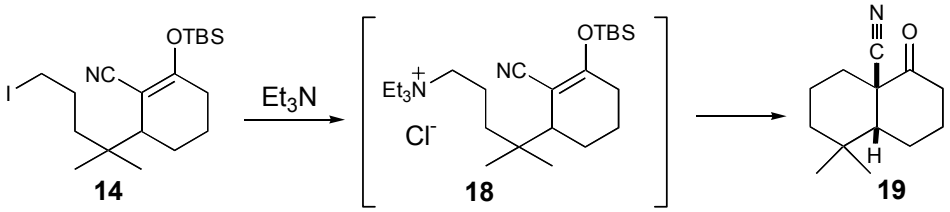

The cyclization stereoselectivity is particularly intriguing. Exclusive formation of the *trans*-decalins **3** and **17** requires cyclization through the boat conformation **4a**, where the nucleophilic π orbitals are directly oriented toward the electrophilic carbonyl group.

Although energetically more accessible, conformer **4b** is unable to cyclize since the nucleophilic π-orbitals are inclined away from the electrophilic aldehyde. In contrast, confomer **4c** has an ideal orbital alignment leading to a *cis*-fused decalin whose absence suggests that a rapid retro-Mukaiyama reaction causes equilibriation to the *trans*-decalin system.

Potentially decalin **3** could also arise by cleavage of the silyl ether followed by enolate cyclization,[136] although this appears less likely since premature workup affords none of the anticipated ketonitrile. Evidence for an equilibriation comes from thermolysis of **17**. Separating the epimeric alcohols and resubjecting **17** containing an axial alcohol, to the same reaction conditions converges **17** to the equatorial epimer **3**. This equilibriation most likely involves a retro-aldol reaction followed by re-cyclization through a boat-like transition state to afford the more stable alcohol.

The use of *i*-$Pr_2NEt$ at lower temperatures is crucial since less hindered bases, such as triethylamine, at higher temperatures lead predominantly to the *cis*-decalin, **19 (**Scheme 5**)**. Presumably, $Et_3N$ is a more effective nucleophile than DMSO, causing Mukaiyama cyclization to **19** through the ammonium salt **18**. Fortunately, *i*-$Pr_2NEt$ is sufficiently non-nucleophilic to prevent this premature cyclization allowing efficient access to the

**Scheme 5. Cyclization to a *cis*-Decalin**

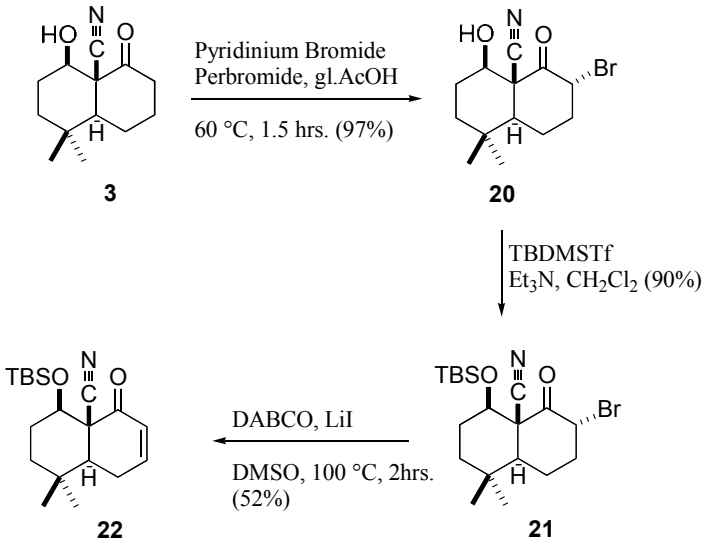



desired decalin **3**.

Access to the *trans*-decalin **3** is significant since **3** contains all but two of the carbons of Kuehneromycin. Installation of the requisite unsaturation inherent in Kuehneromycin proved difficult since the deprotonation of the protected alcohol proved particularly challenging. Recourse was therefore made towards enolization under acidic conditions and interception of the enol with pyridinium bromide perbromide in glacial acetic acid at

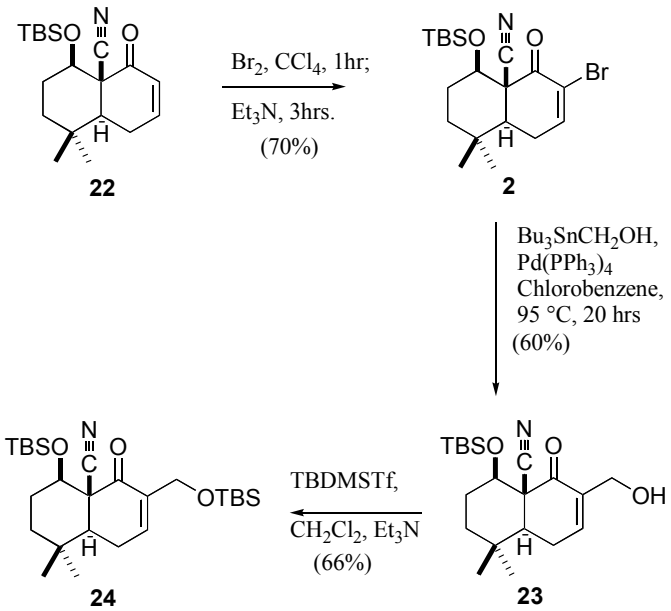
70 °C.[137] Careful monitoring of the reaction time provided good yields of the bromide **20**, whereas extended reaction times afforded significant acetylation of the secondary alcohol. Silylation of **20** provided **21** and was required prior to the HBr elimination to prevent retro-aldol fragmentation (Scheme 6). Dehydrogenation of **21** with lithium carbonate and lithium bromide in DMF introduced the desired unsaturation in the B-ring in a modest yield. Eventually the more soluble amine base DABCO in combination with LiI in DMSO was found to give an improved yield of (52 %) the desired enone **22**.

**Scheme 6. Installation of Unsaturation in Ring B**



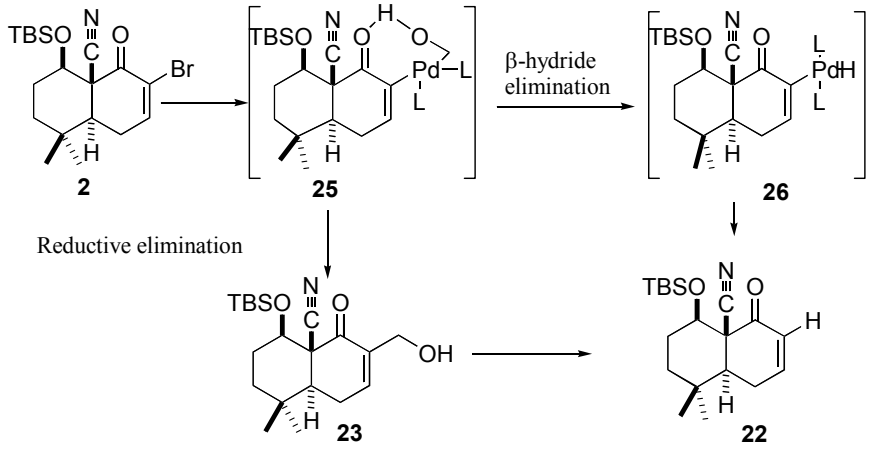

With the successful introduction of unsaturation in ring B, the next goal was to install the remaining two carbons of Kuehneromycin. Several strategies are available for introducing a hydroxy methyl functionality into an enone, often via bromination-ketalization by a circuituous route involving lithium-halogen exchange and formylation.[158] An unexplored but potentially more direct route is through α-bromination[138] followed by Stille coupling with tributyltinmethanol.[139] Initial investigations using tributyltin methanol and tetrakis(triphenylphosphine)palladium(0) afforded the desired α-hydroxymethyl enone **23** in a 1:1 ratio with **22**.[140] Attempts to avoid this reduced material by coupling **2** with $Bu_3SnCH_2OMOM$ afforded only recovered starting material indicating that the free alcohol in the tin reagent was apparently necessary for the coupling to occur (Scheme 7).

**Scheme 7. Installation of the α-Hydroxymethyl Group**



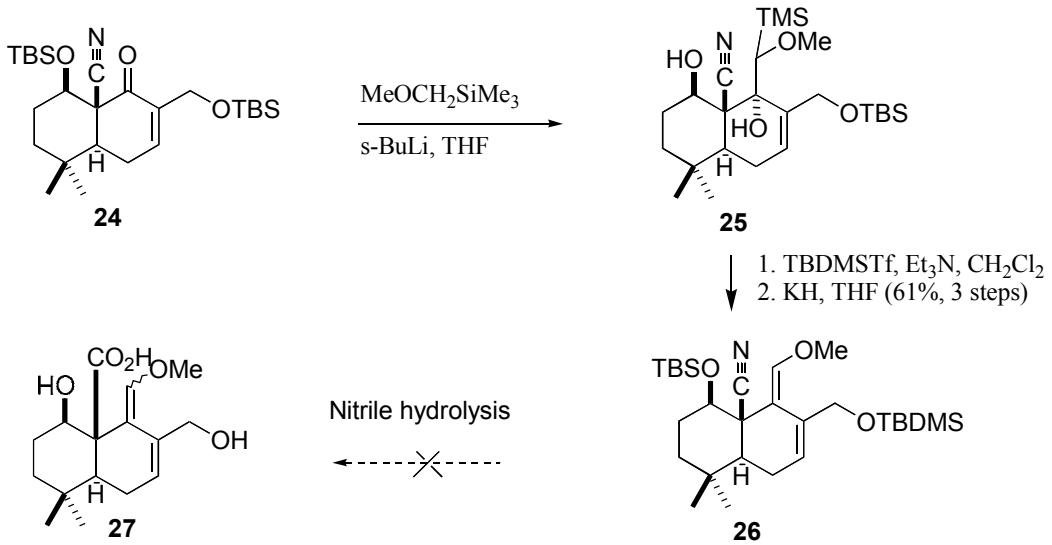

Screening a range of palladium sources and ligands identified the used of non-polar, non-coordinating solvents in providing an improved ratio of the coupled product **23**. The general order of decreasing efficacy was benzene, toluene, heptane, THF and dioxane. Collectively, the combination of a non-polar, poor donor solvent suggests that the tributyltin methanol facilitates the reaction by hydrogen-bonding with the ketone. This internal hydrogen bond would facilitate access to the *cis* stereochemistry required for the reductive elimination from **25** leading to the coupled enone **23** (Scheme 8). In the presence of hydrogen donor solvents there is a competition for intermolecular, rather than intramolecular, bonding that may lead to more of the trans orientation, thereby providing a greater opportunity for β-hydride elimination leading to the palladium hydride **26** and ultimately to the enone **22**. In addition, better donor solvents, such as THF and dioxane, favor co-ordination with Pd that may retard the difficult oxidative addition into the carbon-bromine bond. Assuming a mildly polar, non-coordinating solvent to be optimal, chlorobenzene was identified as the solvent of choice, routinely affording the α-hydroxymethyl enone **23** in 60 % yield.

**Scheme 8 Potential Mechanism for Pd-Coupling of 2**




Installation of the last carbon of the Kuehneromycin skeleton was envisioned through a Peterson olefination.[141] Preliminary olefinations on the free alcohol **23** afforded a variety of products, presumably caused by formation of the allylic alkoxide. Simply protecting the allylic alcohol as the TBS ether **24** allowed the carbonyl addition, though the reaction required an excess of reactant and afforded **25** in which concomitant desilylation of the secondary TBS ether has occurred. Surprisingly the alkoxide intermediate derived from **25** did not eliminate in-situ perhaps because of the transient formation of a silicate from the alkoxide and $SiMe_3$ groups.[142] Support for the formation of a silicate intermediate

**Scheme 9. Peterson Olefination Forrays**

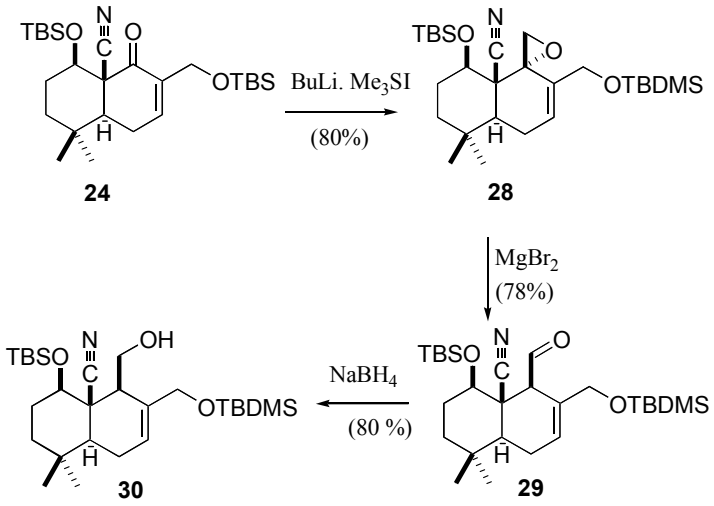



stems from the inability to cause the direct elimination with KH whereas reprotection of **25** as a TBS ether allows a smooth elimination with KH to afford **26** (Scheme 9).

With the Kuehneromycin skeleton in place, attention was focused on the hydrolysis of the angular nitrile **26**→**27** (Scheme 9). Screening numerous procedures[143] for the hydrolysis of the nitrile proved fruitless, as were analogous hydrolyses on earlier intermediates. Similarly, attempts to reduce the nitrile with *i*-$Bu_2AlH$ or $LiAlH_4$[143] either led to recovered, unreacted nitrile or caused extensive decomposition. The problem appears to be the significant steric hindrance of the nitrile combined with a sensitivity of the methoxy diene that leads to significant decomposition.

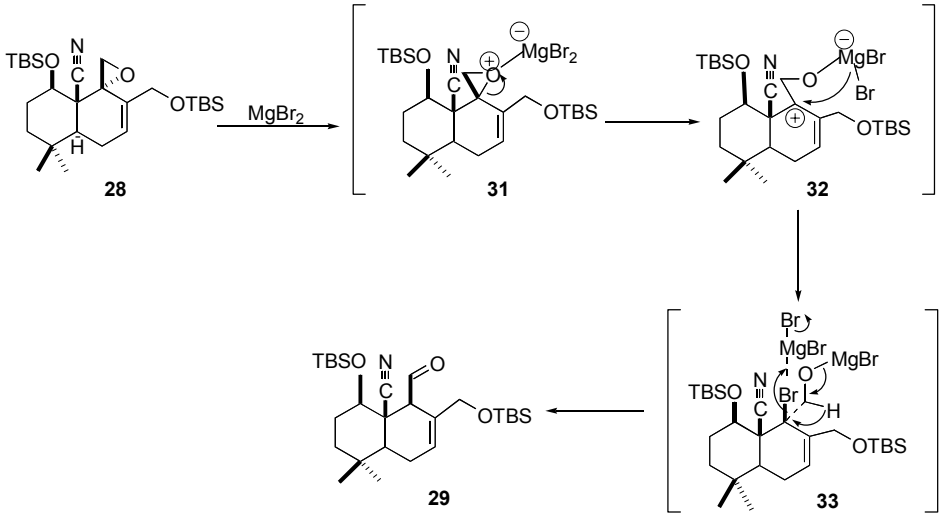
An attractive solution to overcome the steric hindrance is an intramolecularly assisted hydrolysis. The plan was to install a hydroxymethyl group adjacent to the nitrile to facilitate an intramolecular hydrolysis while maintaining the olefin position in ring B. Introducing the requisite hydroxymethyl group provided insight into the Lewis acid rearrangement of epoxides to aldehydes.[144] Addition of the ylide obtained from n-butyl lithium and trimethylsulfonium iodide[145] to the ketone **24**, affords the desired epoxide **28** in high yield. Rearrangement of the epoxide to the corresponding aldehyde **29** (Scheme 10) was effective with a range of Lewis acids ($MgBr_2$, $ZnCl_2$, $TiCl_4$, $BF_3.OEt_2$) which afforded distinct preferences for the α and β-aldehydes.[146] The α-stereochemistry of **29** proved crucial since the thermodynamic product was the epimeric, axial, β-aldehyde that is presumably favored in order to prevent eclipsing with the adjacent equatorial TBS ether.[156]

**Scheme 10. Epoxide Route to Hydroxymethyl Decalin 26**



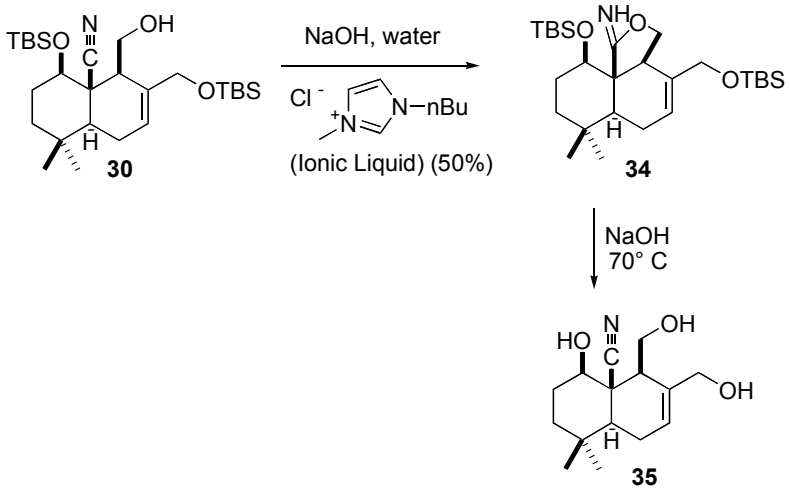

Formation of the desired equatorial aldehyde was favored with $MgBr_2$. Optimization experiments revealing the need for 2 equivalents of $MgBr_2$ which caused substantial epimerization. Significantly, an intermediate bromohydrin **33** was detected leading to a procedure where complete conversion to the bromohydrin was achieved by adding 0.5 equivalents of $MgBr_2$ followed by a further 1.5 equivalents after 30 minutes. Mechanistically, the addition of the initial 0.5 equivalents of $MgBr_2$ likely leads to the bromohydrin intermediate **33**, by an initial coordination through **31**, triggering a facile epoxide opening to the planar carbocation **32** that is subsequently intercepted by bromide from the more accessible α-face. Surprisingly the isolation of the bromohydrin appears to be the first time that the intermediate has ben identified in this arrangement. Addition of excess $MgBr_2$ allows the activation of the newly installed bromide that is then ejected during the backside[147] hydride migration through **33**.[148] Presumably the other Lewis acids act in a similar manner to generate an intermediate analogous to **32** that is not intercepted by a halogen but instead directly suffers hydride migration across the α-face to generate the β-aldehyde (Scheme 11).

**Scheme 11. Epoxide Rearrangement Mechanism**




Simple sodium borohydride reduction of the aldehyde affords the desired alcohol **30**.[157] Installation of the proximal hydroxy group now allowed an evaluation of the internally-promoted hydrolysis. Screening an array of hydroxide sources in protic and aprotic solvents led to either minimal hydrolysis or extensive decomposition. Reasoning that a polar solvent was required to polarize the nitrile's electron cloud, thereby rendering the carbon more electrophilic, the hydrolysis in the ionic liquid, 1-butyl-3-methyl imidazolyl chloride was tried. Significantly, the use of NaOH in the ionic liquid at room temperature afforded the iminolactone **34**[149] in addition to an equal quantity of recovered starting material **30**.

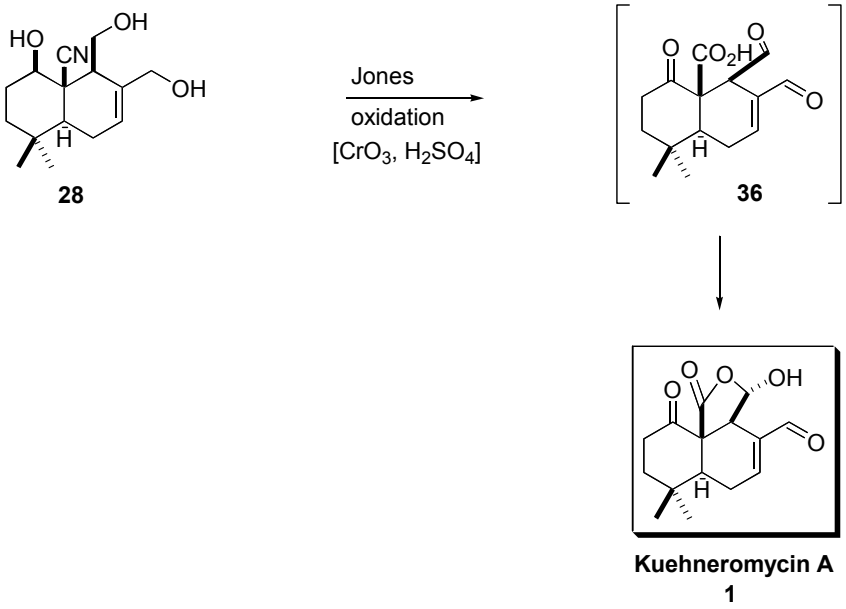
**Scheme 12. Nitrile hydrolysis in an ionic liquid**



Although the intramolecular hydrolysis proved successful, further hydrolysis was surprisingly difficult. More vigorous acidic and basic hydrolysis causes the iminolactone **34**[150] to fragment to a material tentatively identified as the nitrile alcohol **35**, presumably by deprotonation of the imine nitrogen followed by ejection of alkoxide.[155] The more vigorous hydrolytic conditions in the ionic liquid cause simultaneous cleavage of the silyl ether groups.

With small quantities of the nitrile triol available, the material was oxidized in the hope of selectively installing the ketone in ring A that might prove less sterically congested and more amenable to hydrolysis. Surprisingly, exposing the nitrile triol **35** to the Jones reagent[134] at 0 °C (15-30 min) caused the complete consumption of **35** resulting in a crude NMR spectra with signals overlapping with those of Kuehneromycin A. Tentative confirmation for the presence of Kuehneromycin was obtained by High Resolution Mass Spectrometry (HRMS), although optimization of the oxidative conversion of **35** to Kuehneromycin proved elusive.

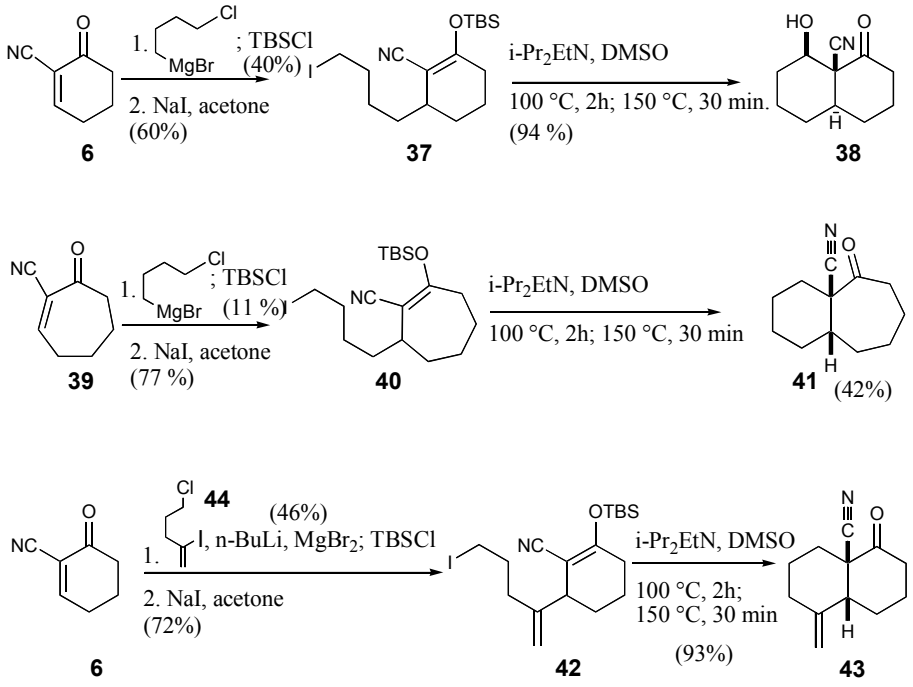
**Scheme 13. Novel Oxidation of Nitrile Alcohol 28**




## 2.4 Oxidative Cyclizations

The synthesis route to Kuehneromycin uncovered an unusual oxidative cyclization (Scheme 4). The value of this cyclization, in stereoselectively installing two new stereocenters, stimulated the brief development of this methodology. Using essentially the same conjugate addition-silylation followed by Finkelstein iodination, the three cyclization substrates **37, 40** and **42** were probed to explore the generality of the cyclization (Scheme 14). The cyclization of **37** is as efficient as that of the synthesis intermediate **14**, although the 7-membered ring analog afforded an impure mixture of oxidative cyclization and the deoxo-product arising from premature cyclization (Scheme 14). Surprisingly the cyclization of **42** only afforded the *cis*-deoxonitrile **43**, possibly as a result of adventitious water.

**Scheme 14. Oxidative Cyclizations**

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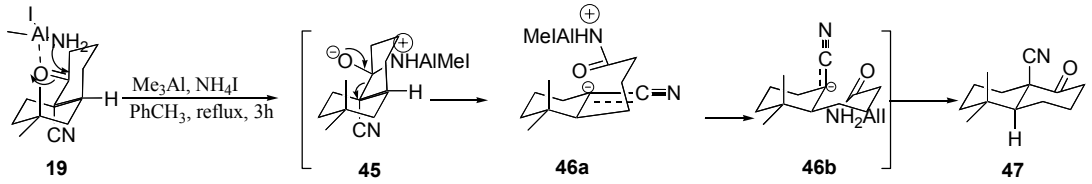
## 2.5 Isomerization of Quaternary Centers

Difficulties with the nitrile hydrolysis initiated a series of model hydrolyses with remarkable results. An excellent model appeared to be the *cis*-decalin **19**, generated as an undesired minor component during optimization of the oxidative cyclizations (Scheme 5). Although hydrolyses under acid or basic conditions were unsuccessful, an attempt at generating the amidine[151] caused the remarkable equilibration of **19** to the corresponding *trans*-decalin **47**. The unprecedented isomerization may occur by aluminum coordination

to the ketone oxygen followed by attack of the amide nitrogen onto the carbonyl to generate the alkoxide **45**. Retro aldol-type fragmentation would generate a nitrile anion **46a-b**, and an aluminum amidate that can realign for cyclization to the thermodynamically more stable *trans*-decalin **47** (Scheme 15). The novelty of this equilibration was tempered by finding that the reaction is substrate specific, failing to equilibriate the *des*-methyl analog.

**Scheme 15. Isomerization of Quarternary Centers**

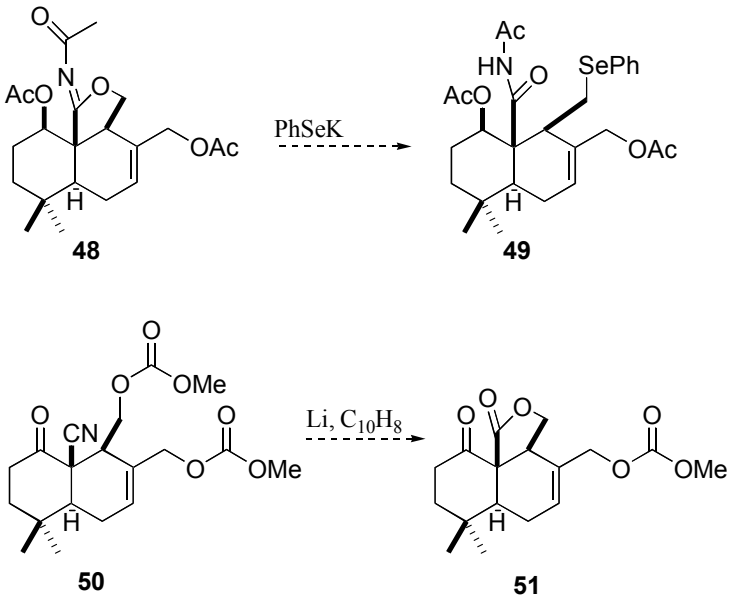



## 3.0 Conclusion

A concise route to advanced Kuehneromycin A intermediates has been developed that is expected to facilitate completion of the synthesis. Formation of the key decalin **3** through a novel Kornblum oxidation-Mukaiyama aldol is particularly unusual, coupling two distinctly different reactions in a highly stereoselective sequence. Overall the strategy installs all but two carbons of Kuehneromycin in a single operation.

Completion of the synthesis requires solving the dilemma of hydrolysing the hindered nitrile. Several strategies are conceptually possible with the selenide ring opening[152] of **48** (by tris-acetylating nitrile triol **28**) being appealing since this allows a mild, non-basic conversion to selenides that are amenable to oxidative Pummer rearrangements for installing the aldehyde (Scheme 16). Another attractive strategy is to convert the nitrile triol **28**, to the dicarbonate **50** followed by reductive decyanation to generate an enolate for internal acylation.[153] Regardless of the final strategy, access to these advanced intermediates has uncovered valuable insight for the final sequence and simultaneously revealed remarkable new chemistry during model studies.

**Scheme 16. Potential Routes to Kuehneromycin A**




**48** **49**

**50** **51**

## 4. Experimental

Proton nuclear magnetic resonance ($^{1}$H NMR) spectra and carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on a Bruker 300 MHz spectrometer using deuteriochloroform as the solvent. Signal positions are given in parts per million (δ) and were determined relative to the residual proton signal for $CDCl_3$ (δ 7.26) and the carbon signal for $CDCl_3$ (δ 77.0). The $^{1}$H NMR coupling constants (*J*-values) are given in Hz. Spectral content is listed in the following order: chemical shift (δ), multiplicity, coupling constants (Hz), number of protons.

Infrared (IR) spectra were recorded on a Perkin Elmer model 1600 Fourier transform spectrophotometer with internal calibration. The IR spectra of solids and liquids were recorded as films on sodium chloride plates. Mass spectra were recorded on a Varian 3400 series gas chromatograph interfaced to a Saturn II mass spectrometer.

Preparative silica gel thin layer chromatography was performed on commercially available (PF-254), glass backed plates (25 x 25cm), precoated with silica gel 60 to a thickness of 0.5 mm. Visualization of the chromatograms was accomplished with an ultraviolet light (254 nm), heating the chromatogram after staining with commercially available (Aldrich Chemical Co., Inc.) phosphomolybdic acid in ethanol (1:4 ratio), a 5% aqueous solution of ammonium molybdate in 10% aqueous sulfuric acid (w/v), or with an aqueous 5% potassium permanganate solution. Conventional flash chromatography was performed with 230-400 mesh silica gel (E. Merck, Silica gel 60). Radial chromatography was performed on a Chromatotron® with plates prepared in-house with silica gel 60 $PF_{254}$ containing gypsum

Sonication was performed with a Bransonic® ultrasonic cleaner. Melting points were measured on a Mel-Temp II® apparatus and are uncorrected.

All dry solvents were obtained by refluxing over an appropriate drying agent[160]. Distilled solvents were used immediately or stored over molecular sieves where appropriate. Diethyl ether and tetrahydrofuran were dried over sodium benzophenone ketyl.

Unless stated otherwise, all reactions were carried out under an atmosphere of dry nitrogen using glassware that had been thoroughly dried under vacuum.

**5-hexen-2-bromide** (**8**). An ethereal solution of methyllithium (20.3 mL, 7.6 mmol) was added slowly to a –78 °C, THF solution (50 mL) of ketone **7** (2.0 g, 5.06 mmol). After 30 min the solution was poured into a solution of saturated, aqueous $NH_4Cl$. The aqueous phase was extracted with ethyl acetate and the organic layers were washed with brine, dried ($Na_2SO_4$) and concentrated to give 2 g (90 %) of 5-hexen-2-ol as a clear oil. IR (film) 3371, 1633 $cm^{-1}$; $^1H$ NMR δ 1.23 (s, 6H), 1.55-1.60 (m, 3H), 2.11-2.19 (m, 2H), 4.94-5.08 (m, 2H), 5.79-5.92 (m, 1H); $^{13}C$ NMR δ 28.7, 29.2, 42.8, 114.3, 139.0; GC/MS 115 (M+H). Neat phosphorus tribromide (1.96 mL, 10.8 mmol) was added slowly to a room temperature, $CH_2Cl_2$ solution (20 mL) of 5-hexen-2-ol (1.1 g, 9.79 mmol). After 3 h, the reaction mixture was poured into water, the aqueous phase was extracted with $CH_2Cl_2$ and the combined organic extracts were washed with brine and dried ($Na_2SO_4$). Evaporation of the organic extracts gave 0.85 g of spectroscopically pure **8** as a yellow oil (49 %): IR (film), 1642 $cm^{-1}$; $^1H$ NMR δ 1.77 (s, 6H), 1.85-1.92 (m, 2H), 2.25-2.32 (m, 2H), 4.96-5.10 (m, 2H), 5.77-5.90 (m, 1H); $^{13}C$ NMR δ 30.5, 33.8, 46.8, 67.5, 115.0, 137.5; GC/MS 176.

**2-(*tert*-Butyl-dimethyl-silanyloxy)-6-(1,1-dimethyl-pent-4-enyl)-cyclohex-1-enecarbonitrile (9)**. THF (10 mL) was added to a mixture of finely chopped lithium metal (60 mg, 8.36 mmol) and naphthalene (114 mg, 0.89 mmol) to afford a dark green solution. A THF solution (20 mL) of zinc chloride (0.570 g, 4.18 mmol) was added slowly and then the reaction was heated to reflux. After 1 h, the reaction was allowed to cool, the finely divided zinc was allowed to settle, the supernatant was removed, and the black zinc was washed twice with THF. After dipersing the zinc in THF (20 mL), a THF solution (10 mL) of the bromide **8** (0.22 g, 1.2 mmol) was slowly added and the mixture was then heated to reflux. After 2 h the solution was cooled to room temperature and added slowly to a solution of the ketonitrile **6** (0.12 g, 1.0 mmol) in THF (20 mL) at –78 °C. After 4 h, TBSCl (0.23 g, 1.52 mmol) was added to the reaction mixture and then the mixture was allowed to warm to room temperature overnight. The reaction was then poured into a saturated, aqueous, solution of $NH_4Cl$, the organic layer was extracted (EtOAc) and washed with brine and dried ($Na_2SO_4$). Evaporation of the organic extracts

and radial chromatography of the resulting oil (1:19 EtOAc /hexanes) gave 0.18 g (55%) of **9** as a yellow oil: IR (film) 2206, 1607 $cm^{-1}$; $^{1}H$ NMR δ 0.22 (s, 3H), 0.24 (s, 3H), 0.98 (s, 9H), 1.04 (s, 6H), 1.34-2.18 (m, 10H), 2.36 (t, *J*= 6 Hz, 1H), 4.90-5.04 (m, 2H), 5.75-5.88 (m, 1H); $^{13}C$ NMR δ -4.2, -4.2, 17.6, 20.6, 23.5, 24.9, 25.1, 25.2, 25.6, 27.9, 30.7, 36.6, 39.4, 42.7, 92.6, 113.5, 119.7, 138.7, 168.0.

**2-(*tert*-Butyl-dimethyl-silanyloxy)-6-(1,1-dimethyl-4-oxo-butyl)-cyclohex-1-enecarbonitrile (4).** Solid osmium tetroxide (0.87 mg, 3 μmol) was added to a THF-$H_2O$ solution (9:1, 10 mL) of the alkene **9** (114 mg, 0.342 mmol). After 5 min, the mixture became dark brown and sodium periodate (154 mg, 0.720 mmol) was then added in portions over 30 min. After 1.5 h the solution was extracted with EtOAc and the organic extracts were dried ($Na_2SO_4$) and concentrated to give, after radial chromatography, (1:19 EtOAc/hexanes) 93 mg (82 %) of **4** as a colorless oil: IR (film) 2710, 2205, 1725, 1606 $cm^{-1}$; $^{1}H$ NMR 0.23 (s, 3H), 0.28 (s, 3H), 1.03 (s, 12H), 1.08 (s, 3H), 1.41-2.60 (m, 11H), 9.75 (s, 1H); $^{13}C$ NMR δ -4.13, 17.7, 20.7, 23.6, 25.1, 25.5, 29.3, 30.7, 31.7, 36.3, 38.7, 40.2, 42.8, 92.1, 168.6.

**4-hydroxy-1,1-dimethyl-5-oxo-octahydro-naphthalene-4a-carbonitrile (3 + 10).** A THF solution of tetrabutylammonium fluoride (0.09 mL, 0.09 mmol) is added to a THF room temperature solution (3 mL) of the aldehyde **4** (20 mg, 0.06 mmol). After 1h the solution was extracted with EtOAc and the organic extracts were dried over $Na_2SO_4$ and concentrated to give, after radial chromatography (2:3 EtOAc/hexanes), 2.5 mg (22%) each of **3** and 2.5 mg (22%) of **10**. The structure and stereochemistry of **3** and **10** were determined after derivatization as TBS-ethers to **3b** and **10b** respectively. For **4-(*tert*-Butyl-dimethyl-silanyloxy)-1,1-dimethyl-5-oxo-octahydro-naphthalene-4a-carbonitrile (3b)**, neat pyridine (2.2 μL, 0.028 mmol) and TBS-triflate (3.8 μL, 0.017 mmol) were added sequentially to a room temperature $CH_2Cl_2$ solution (1 mL) of **3** (2.5 mg, 0.011 mmol). After 12 h the reaction was poured into a saturated, aqueous, solution of sodium bicarbonate, the aqueous phase was extracted with $CH_2Cl_2$ and then the combined extracts were washed with brine and dried ($Na_2SO_4$). Concentration of the organic extract followed by radial chromatography (19:1 EtOAc / hexanes) gave 3.1 mg

(90 %) of **3b** as an white crystalline solid (mp. 273-275) whose structure was proven by crystallographic diffraction (Appendix 1): IR (film) 2232, 1737 $cm^{-1}$; $^1H$ NMR δ 0.09 (s, 3H), 0.11 (s, 3H), 0.85 (s, 9H), 0.91 (s, 3H), 1.15 (s, 3H), 1.18-2.05 (m, 8H), 2.17-2.24 (m, 1H), 2.36-2.39 (m, 1H), 3.07 (ddd, *J*=19, 13, 7 Hz, 1H), 4.00 (dd, *J*=11, 5Hz, 1H); $^{13}C$ NMR δ -4.94, -4.22, 17.93, 20.2, 23.7, 25.7, 27.4, 28.7, 31.4, 34.0, 38.6, 39.0, 55.1, 60.3, 69.1, 118.8, 202.5; HRMS (ESI) calcd for M+Na $C_{19}H_{33}NO_2SiNa$ 358.2173 found 358.2155. For **4-(*tert*-Butyl-dimethyl-silanyloxy)-1,1-dimethyl-5-oxo-octahydro-naphthalene-4a-carbonitrile (10b),** using the same protocol as for the synthesis of **3b**, pyridine (2.2 μL, 0.028 mmol) and TBS-triflate (3.8 μL, 0.017 mmol) were added to a $CH_2Cl_2$ solution (1 mL) of **10** (2.5 mg, 0.011 mmol) to afford after radial chromatography (19:1 EtOAc / hexanes) 2.9 mg (83 %) of **10b** as an white crystalline solid (mp. 237-239) whose structure was proven by crystallographic diffraction (Appendix 1): $^1H$ NMR δ 0.03 (s, 3H), 0.08 (s, 3H), 0.86 (s, 9H), 0.93 (s, 3H), 1.32 (s, 3H), 1.51-2.22 (m, 8H), 2.43-2.62 (m, 2H), 4.30 (dd, *J*= 4.1, 9.3 Hz, 1H); $^{13}C$ NMR δ -5.0, -3.9, 17.9, 23.7, 25.0, 25.5, 28.9, 29.6, 29.7, 33.8, 33.9, 37.4, 51.6, 69.7, 119.6, 202.7.

**2-(*tert*-Butyl-dimethyl-silanyloxy)-6-(4-iodo-1,1-dimethyl-butyl)-cyclohex-1-enecarbonitrile (14)**. Neat chloride **13**[128] (2.47 g, 7.0 mmol) was added to room temperature, acetone solution (100 mL) of sodium iodide (5.21 g, 35 mmol) and then the mixture was heated to reflux. After 24 h the reaction was allowed to cool, concentrated, washed with water, extracted with $CH_2Cl_2$ and dried ($Na_2SO_4$). Concentration, and radial chromatography (1:19 EtOAc/hexanes) of the resulting yellow oil, provided 2.82 g (85 %) of **14** as a colorless oil: IR (film) 2205 $cm^{-1}$; $^1H$ NMR δ 0.51 (s, 3H), 0.53 (s, 3H), 1.26 (s, 9H), 1.26 (s, 3H), 1.29 (s, 3H), 1.54-1.89 (m, 4H), 1.99-2.21 (m, 4H), 2.37-2.41 (m, 2H), 2.56-2.61 (m, 1H), 3.30 -3.50 (m, 2H); $^{13}C$ NMR ($C_6D_6$) δ -2.5, 19.2, 25.6, 26.8, 27.2, 37.8, 43.1, 44.3, 94.6, 193.5; HRMS (ESI) calcd for (M+Na) $C_{19}H_{34}INOSi$ 470.1347, found 470.1351.

**4-Hydroxy-1,1-dimethyl-5-oxo-octahydro-naphthalene-4a-carbonitrile (3)**. A DMSO solution (1 mL) of **14** (24 mg, 0.054 mmol) and neat *i*-$Pr_2NEt$ (0.05 mL, 0.27 mmol) was

added to a 100 °C solution (5 mL) of DMSO. After 2 h the temperature was increased to 150 °C for a further 30 min and then the flask was then immediately cooled in an ice-water bath. Water was added, the mixture was extracted with EtOAc, and then the organic extracts were washed with brine, dried ($Na_2SO_4$) and concentrated to give a yellow oil. Radial chromatography (2:3 EtOAc/hexanes) yielded 9.5 mg (85 %) of the *trans*-decalin **3** as a colorless oil: IR (film) 3524, 2233, 1724 $cm^{-1}$; $^1H$ NMR δ 0.95 (s, 3H), 1.18 (s, 3H), 1.23-2.01 (m, 7H), 2.18-2.25 (m, 1H), 2.45-2.51 (m, 1H), 2.97 (td, *J*= 13.8, 6.9 Hz, 2H), 3.10 (s, 1H), 3.93 (br t, *J*=8 Hz, 1H); $^{13}C$ NMR δ 20.4, 23.2, 26.3, 31.5, 34.4, 38.8, 53.6, 59.1, 70.4, 117.8, 205.3; MS m/e 222 (M+H); HRMS (ESI) calcd for (M+Na) $C_{13}H_{19}NO_2$ 244.1308, found 244.1300.

**4-Hydroxy-1,1-dimethyl-5-oxo-octahydro-naphthalene-4a-carbonitrile (17).** A DMSO solution of **14** (24 mg, 0.054 mmol) and *i*-$Pr_2NEt$ (0.05 mL, 0.27 mmol) were added in one portion to a flask containing DMSO at 100 °C. After 2 h the temperature was increased to 150 °C for a further 10 min. The flask was then immediately cooled in an ice-water bath. Water was added, the mixture was extracted with EtOAc, and the organic extracts were washed with brine, dried ($Na_2SO_4$) and concentrated to give a yellow oil. Radial chromatography (2:3 EtOAc/hexanes) yielded 9.5 mg (85 %) of the *trans*-decalin **17**. IR (film) 3560, 2229, 1720 $cm^{-1}$; $^1H$ NMR δ 0.99 (s, 3H), 1.18 (s, 3H), 1.56-2.22 (m, 8H), 2.40-2.49 (m, 1H), 2.94 (td, *J*= 14, 7 Hz, 2H), 3.44 (s, 1H), 4.44-4.45 (m, 1H); $^{13}C$ NMR δ 20.4, 23.0, 25.4, 25.8, 31.8, 33.3, 34.2, 39.3, 47.8, 67.2, 118.7, 206.2; MS m/e 222 (M+H); HRMS (ESI) calcd for (M+Na) $C_{13}H_{19}NO_2$ 244.1308, found 244.1298.

**1,1-dimethyl-5-oxo-octahydro-naphthalene-4a-carbonitrile (19).** A DMSO solution of **14** (27 mg, 0.06 mmol) and $Et_3N$ (0.04 mL, 0.3 mmol) were added in one portion to a flask containing DMSO at 150 °C. After 10 min, the flask was immediately cooled in an ice-water bath. Water was added, the mixture was extracted with EtOAc, and the organic extracts were washed with brine, dried ($Na_2SO_4$) and concentrated to give a yellow oil.

Radial chromatography (2:3 EtOAc/hexanes) yielded 8 mg (75 %) of the decalin **19** spectroscopically identical to material prepared previously.[128]

**6-Bromo-4-hydroxy-1,1-dimethyl-5-oxo-octahydro-naphthalene-4a-carbonitrile (20).** Solid pyridinium bromide perbromide (186 mg, 0.58 mmol) was added to a glacial acetic acid solution (10 mL) of the *trans*-decalin **3** (110 mg, 0.530 mmol). After immersing in a 60 °C sand bath for 20 min, the reaction was cooled to room temperature, diluted with water, and poured carefully into a cold, saturated, aqueous solution of sodium bicarbonate. The resulting mixture was extracted with EtOAc and the combined organic extracts were washed with $NaHCO_3$, and brine, and then dried ($Na_2SO_4$). The organic extracts were then concentrated, redissolved in EtOAc and filtered through a short pad of silica gel to give 146 mg (97 %) of the α bromo-ketone **20**: IR (film) 2233, 1752 $cm^{-1}$; $^1H$ NMR δ 0.11 (s, 3H), 0.13 (s, 3H), 0.85 (s, 9H), 0.93 (s, 3H), 1.15 (s, 3H), 1.19-1.36 (m, 4H), 1.50 (dt, *J*= 14.0, 3.5 Hz, 1H), 1.74-2.18 (m, 6H), 2.69-2.78 (m, 1H), 4.06-4.13 (m, 1H), 5.28 (dd, *J*= 12.4, 6.6 Hz, 1H); $^{13}C$ NMR δ -4.9, -4.3, 17.9, 20.2, 25.0, 25.7, 28.7, 31.3, 34.1, 38.4, 39.2, 52.1, 54.5, 60.4, 69.7, 118.0, 194.0.

**6-Bromo-4-(*tert*-Butyl-dimethyl-silanyloxy)-1,1-dimethyl-5-oxo-octahydro-naphthalene-4a-carbonitrile (21).** Neat $Et_3N$ (1.09 mL, 7.80 mmol) and TBSOTf (1.78 mL, 6.6 mmol) were added sequentially to a room temperature $CH_2Cl_2$ solution (40 mL) of **20** (1.8 g, 6.0 mmol). After 12 h the reaction was poured into a saturated, aqueous, solution of sodium bicarbonate, the aqueous phase was extracted with $CH_2Cl_2$ and then the combined extracts were washed with brine and dried ($Na_2SO_4$). Concentration of the organic extract followed by radial chromatography (1:9 EtOAc / hexanes) gave 2.23 g (90 %) of **21** as an oil: IR (film) 2233, 1752 $cm^{-1}$; $^1H$ NMR δ= 0.11 (s, 3H), 0.13 (s, 3H), 0.85 (s, 9H), 0.93 (s, 3H), 1.15 (s, 3H), 1.19-1.36 (m, 4H), 1.50 (dt, *J*= 14.0, 3.5 Hz, 1H), 1.74-2.18 (m, 6H), 2.69-2.78 (m, 1H), 4.06-4.13 (m, 1H), 5.28 (dd, *J*= 12.4, 6.6 Hz, 1H); $^{13}C$ NMR δ -4.9, -4.3, 17.9, 20.2, 25.0, 25.7, 28.7, 31.3, 34.1, 38.4, 39.2, 52.1, 54.5, 60.4, 69.7, 118.0, 194.0.

**4-(*tert*-Butyl-dimethyl-silanyloxy)-1,1-dimethyl-5-oxo-1,3,4,5,8,8a-hexahydro-2*H*-naphthalene-4a-carbonitrile (22).** A DMSO solution (15 mL) of **21** (43 mg, 0.10 mmol), lithium iodide (28 mg, 0.21 mmol) and DABCO (29 mg, 0.26 mmol) were heated at 100 °C. After 2h the reaction was cooled, filtered through a pad of silica, concentrated, and purified by radial chromatography (1:9 EtOAc/hexanes) to afford 18 mg (52 %) of **22** as an oil: IR (film) 2221, 1690 $cm^{-1}$; $^1H$ NMR δ 0.14 (s, 3H), 0.17 (s, 3H), 0.89 (s, 9H), 0.94 (s, 3H), 1.19 (s, 3H), 1.22-1.39 (m, 2H), 1.50 (dt, *J*= 13.9, 3.5 Hz, 1H), 1.74 (dd, *J*= 11.0, 4.1 Hz, 1H), 1.78- 1.88 (m, 1H), 2.48 (dt, *J*= 20, 5 Hz, 1H), 2.74 (ddt, *J*= 20, 11, 2.7 Hz, 1H), 3.89-3.94 (m, 1H), 5.99-6.04 (m, 1H), 6.98 (ddd, *J*= 10, 6, 2 Hz, 1H); $^{13}C$ NMR δ -4.8, -4.1, 18.1, 20.4, 25.8, 26.4, 29.1, 30.4, 33.4, 38.4, 49.1, 54.5, 69.3, 116.5, 126.9, 148.8, 191.1; HRMS (ESI) calcd for (M+Na) $C_{19}H_{31}NO_2Si$ 356.2016, found 356.1994.

**6-Bromo-4-(*tert*-butyl-dimethyl-silanyloxy)-1,1-dimethyl-5-oxo-1,3,4,5,8,8a-hexahydro-2*H*-naphthalene-4a-carbonitrile (2)**. A $CCl_4$ solution of bromine (0.77 mL, 0.77 mmol) was added, dropwise, to a room temperature, $CCl_4$ solution (10 mL) of the enone **22** (255 mg, 0.77 mmol). After 1h, triethylamine (0.41 mL, 3.07 mmol) was added and after a further 2h the reaction was filtered through a pad of silica, concentrated, and purified by radial chromatography (1:9 EtOAc/hexanes) to give 220 mg (70 %) of **2** as a colorless oil: IR (film) 2235, 1717, 1613 $cm^{-1}$; $^1H$ NMR δ 0.14 (s, 3H), 0.19 (s, 3H), 0.89 (s, 9H), 0.94 (s, 3H), 1.18 (s, 3H), 1.20-1.33 (m, 1H), 1.51 (dt, *J*= 13.9, 3.5 Hz, 1 H), 1.77-1.86 (m, 3H), 2.53 (ddd, *J*=19.5, 6, 4 Hz, 1H), 2.80 (ddd, *J*= 19.5, 11, 2.7 Hz, 1H) 3.95 (dd, *J*= 9.5, 7.2 Hz, 1H), 7.36 (dd, *J*= 6, 3 Hz, 1H); $^{13}C$ NMR δ -4.8, -4.2 18.0, 20.4, 25.8, 28.5, 29.1, 30.3, 33.4, 38.2, 48.6, 55.1, 69.8, 115.5, 119.2, 149.0, 184.6.

**4-(*tert*-Butyl-dimethyl-silanyloxy)-6-hydroxymethyl-1,1-dimethyl-5-oxo-1,3,4,5,8,8a-hexahydro-2*H*-naphthalene-4a-carbonitrile (23).** A chlorobenzene solution (10 mL) of bromoenone **2** (10.7 mg, 0.026 mmol), tributyltinmethanol (10 mg, 0.031 mmol) and $Pd(PPh_3)_4$ (3 mg, 2 μmol) was heated to 95 °C. After 3 h, additional $Pd(PPh_3)_4$ (1.5 mg, 1 μmol) was added and after 4h the reaction mixture was cooled and then filtered through a pad of Celite. Concentration of the solution and radial chromatography (2:3 EtOAc/ hexanes) gave 5.6 mg (60 %) of the coupled product **23** as a colorless oil: IR (film) 3486,

2234, 1698, 1648 $cm^{-1}$; $^1H$ NMR δ 0.13 (s, 3H), 0.16 (s, 3H), 0.88 (s, 9H), 0.93 (s, 3H), 1.17 (s, 3H), 1.20-1.31 (m, 1H), 1.45 (dt, *J*= 17, 3 Hz, 1H), 1.58-1.88 (m, 3H), 2.26 (s, 1H), 2.46-2.76 (m, 2H), 3.92 (dd, *J*= 9, 8 Hz, 1H), 4.24 (ABq, Δν=52 Hz, *J*=13.5 Hz, 2H), 6.94 (d, *J*= 4.6 Hz, 1H); $^{13}C$ NMR δ -4.1, 18.0, 20.4, 25.8, 26.0, 29.1, 30.3, 33.4, 38.4, 49.1, 54.4, 61.5, 69.3, 116.3, 136.1, 144.7, 192.2; MS m/e 363 (M); HRMS (ESI) calcd for (M+Na) $C_{20}H_{33}NO_3Si$ 386.2122, found 386.2145.

**4-(*tert*-Butyl-dimethyl-silanyloxy)-6-(*tert*-butyl-dimethyl-silanyloxymethyl)-1,1-dimethyl-5-oxo-1,3,4,5,8,8a-hexahydro-2*H*-naphthalene-4a-carbonitrile (24).** Neat triethylamine (15 μL, 0.11 mmol) and TBSOTf (22 μL, 0.083 mmol) were added, sequentially to a room temperature, $CH_2Cl_2$ solution (10 mL) of **23** (20 mg, 0.055 mmol). After 2 h the reaction mixture was poured into a saturated, aqueous, solution of sodium bicarbonate, the aqueous phase was extracted with $CH_2Cl_2$ and then the combined organic extracts were washed with brine and dried ($Na_2SO_4$). Concentration and radial chromatography (1:19 EtOAc/hexanes) afforded 17.2 mg (66 %) of **24** as an oil: IR (film) 2234, 1694 $cm^{-1}$; $^1H$ NMR δ 0.07 (s, 3H), 0.08 (s, 3H), 0.13 (s, 3H), 0.16 (s, 3H), 0.88 (s, 9H), 0.91 (s, 9H), 0.93 (s, 3H), 1.18 (s, 3H), 1.22-1.39 (m, 1H), 1.52 (dt, *J*= 14, 3.4 Hz, 1 H), 1.66-1.90 (m, 3H), 2.48-2.80 (m, 2H), 3.88-3.94 (m, 1 H), 4.23 (d, *J*= 15 Hz, 1H), 4.38 (dd, J= 15, 2.1 Hz, 1 H), 6.93- 6.97 (m, 1H); $^{13}C$ NMR δ -5.5, -5.4, -4.7, -4.2, 18.1, 18.3, 20.5, 25.8, 25.9, 29.2, 30.3, 33.4, 38.4, 49.3, 54.4, 60.2, 69.3, 116.5, 136.3, 142.2, 191.0; HRMS (ESI) calcd for (M+Na) $C_{26}H_{47}NO_3Si_2$ 500.2987, found 500.2983.

**4-(*tert*-Butyl-dimethyl-silanyloxy)-6-(*tert*-butyl-dimethyl-silanyloxymethyl)-5-methoxymethylene-1,1-dimethyl-1,3,4,5,8,8a-hexahydro-2*H*-naphthalene-4a-carbonitrile (26).** A hexanes solution of *s*-BuLi (0.12 mL, 0.16 mmol) was added slowly to a –78 °C, THF solution (3 mL) of $MeOCH_2SiMe_3$ (0.03 mL, 0.16 mmol) . After the addition the reaction was warmed to -25 °C and, after 45 min, cooled to –78 °C. A THF solution (2 mL) of **24** (15 mg, 0.031 mmol) was added and the reaction was then allowed to warm to room temperature overnight. The reaction mixture was then poured into water, extracted with ethyl acetate, and concentrated. The yellow residue was dissolved in $CH_2Cl_2$ and then neat $Et_3N$ (10 μL, 0.08 mmol) and TBSOTf (12 μL, 0.046 mmol)

were added. After 1 h, the reaction mixture was poured into water, extracted with $CH_2Cl_2$, redissolved in THF (2 mL) and added to a room temperature suspension of KH (8 mg, 15 μmol) in THF (5 mL). After 3 h, the mixture was poured into saturated aqueous ammonium chloride, the aqueous phase extracted with ethyl acetate, and the combined organic extracts washed with brine and dried ($Na_2SO_4$). Purification by radial chromatography (1:9 EtOAc/hexanes) gave 15.2 mg (61%) of **26** as an oil: IR (film) 3518, 2231, 1631 $cm^{-1}$; $^1H$ NMR δ 0.07 (s, 3H), 0.09 (s, 3H), 0.91 (s, 12H), 1.10 (s, 3H), 1.13-2.23 (m, 5H), 2.27- 2.50 (m, 2H), 3.78 (s, 3H), 3.97 (pent, *J*= 5 Hz, 1H), 4.16 (ABq Δν= 37 Hz, *J*=12 Hz, 2H), 4.64 (d, *J*= 4.1 Hz, 1H), 5.81 (br s, 1H), 6.56 (s, 1H); $^{13}C$ NMR δ -5.3, -5.1, 18.2, 20.7, 25.5, 25.7, 27.3, 31.3, 33.2, 39.3, 47.5, 48.4, 61.4, 66.8, 70.9, 114.3, 119.5, 125.9, 132.4, 143.7; MS m/e 391.

**4-(*tert*-Butyl-dimethyl-silanyloxy)-6-(*tert*-butyl-dimethyl-silanyloxymethyl)-1,1-dimethyl-5-oxirane-1,3,4,5,8,8a-hexahydro-2*H*-naphthalene-4a-carbonitrile (28).**

A hexane solution of *n*-butyl lithium (0.09 mL, 0.11 mmol) was added to a 0 °C suspension of trimethyl sulfonium iodide (26.3 mg, 0.129 mmol) in THF (4 mL), stirred for 10 min and cooled to –78 °C. Neat enone **24** (21.5 mg, 0.045 mmol) was then added and after 1h the reaction was poured onto ice. The aqueous phase was extracted with EtOAc, and the combined extracts were washed with brine and dried ($Na_2SO_4$). Evaporation of solvent under reduced pressure and purification by radial chromatography (1:9 EtOAc/hexanes) gave 18 mg (80 %) of the epoxide **28** as a colorless oil: IR (film) 2235 $cm^{-1}$; $^1H$ NMR δ 0.05 (s, 6H), 0.13 (s, 3H), 0.14 (s, 3H), 0.89 (s, 9H), 0.93 (s, 9H), 1.11 (s, 3H), 1.25 (s, 3H), 1.43-2.38 (m, 7H), 3.11 (d, *J*=4.8 Hz, 1 H), 3.77 (d, *J*=5 Hz, 2H), 3.93 (ABq, Δν=26 Hz, *J*=13 Hz, 2H), 6.23 (s, 1H); $^{13}C$ NMR δ -5.4, -5.1, -4.1, -2.7, 18.2, 20.4, 25.0, 25.8, 26.0, 29.6, 31.0, 32.7, 38.6, 45.5, 47.6, 52.0, 58.5, 61.8, 70.3, 119.0, 131.2, 132.7; MS m/e 491 (M+H); HRMS ESI calcd for (M+Na) $C_{27}H_{49}NO_3Si_2$ 514.3143, found 514.3151.

**4-(*tert*-Butyl-dimethyl-silanyloxy)-6-(*tert*-butyl-dimethyl-silanyloxymethyl)-5-formyl-1,1-dimethyl-1,3,4,5,8,8a-hexahydro-2*H*-naphthalene-4a-carbonitrile (29)**

Solid magnesium bromide (1.8 mg, 0.01 mmol) was added to a dichloroethane solution (3 mL) of the epoxide **28** (9.6 mg, 0.02 mmol) and then the reaction mixture was heated to reflux. After 30 min a dichloroethane solution (2.5 mL) of $MgBr_2$ (5.4 mg, 0.03 mmol) was added. After 1 h the solution was cooled to room temperature, filtered through a short pad of silica gel, and purified by radial chromatography (1:9 EtOAc/hexanes) to give 7.5 mg (78 %) of the aldehyde **29** as a colorless oil: IR (film) 2232, 1717 $cm^{-1}$; $^1H$ NMR δ 0.03 (s, 6H), 0.07 (s, 3H), 0.10 (s, 3H), 0.88 (s, 9H), 0.90 (s, 9H), 0.93 (s, 3H), 1.14 (s, 3H), 1.20-1.96 (m, 5 H), 2.25-2.41 (m, 2H), 2.93 (s, 1H), 3.56 (dd, *J*= 10, 5 Hz, 1H), 3.89 (ABq, Δν=27 Hz, *J*=14 Hz, 2H), 6.07 (s, 1H), 9.71 (d, *J*=4.4 Hz, 1H); $^{13}C$ NMR -5.5, -5.5, -4.0, -3.3, 18.3, 20.8, 24.1, 25.9, 26.0, 29.2, 31.2, 32.8, 39.1, 46.2, 46.3, 59.8, 63.7, 78.2, 118.8, 125.3, 129.0, 198.7; HRMS (ESI) calcd for (M+Na) $C_{27}H_{49}NO_3Si_2$ 514.3143, found 514.3122. Extended reaction time afforded the furan **9-(*tert*-butyl-dimethyl-silanyloxy)-6,6-dimethyl-5,5*a*,6,7,8,9-hexahydro-4H-naphtho[1,2-*c*]furan-9a-carbonitrile:** IR (film), 2230 $cm^{-1}$; $^1H$ NMR δ 0.17 (s, 3H), 0.18 (s, 3H), 0.98 (s, 12H), 1.14 (s, 3H), 1.25-2.08 (m, 7H), 2.42-2.50 (m, 1H), 2.79-2.85 (m, 1H), 3.72 (dd, *J*= 11, 4Hz, 1H), 7.13 (s, 1H), 7.71 (s, 1H); GC/MS 275 (M+H); HRMS (ESI) calcd for M+Na $C_{21}H_{33}NO_2SiNa^+$ 382.2173 found 382.2150.

**4-(*tert*-Butyl-dimethyl-silanyloxy)-6-(*tert*-butyl-dimethyl-silanyloxymethyl)-5-hydroxymethyl-1,1-dimethyl-1,3,4,5,8,8a-hexahydro-2*H*-naphthalene-4a-carbonitrile (30)**. Solid sodium borohydride (2.0 mg, 52 μmol) was added in one portion to a room temperature, ethanolic solution (2 mL) of the aldehyde **29** (13 mg, 0.026 mmol). After 1 h the solvent was removed under reduced pressure, the residue was dissolved in dichloromethane, and then washed with saturated $NH_4Cl$ solution and dried ($Na_2SO_4$). Concentration and purification by radial chromatography (1:4 EtOAc/ hexanes) gave 10.4 mg (80 %) of the alcohol **30** as a colorless oil: IR (film) 3468, 2226 $cm^{-1}$; $^1H$ NMR δ 0.08 (s, 6H), 0.13 (s, 6H), 0.90 (s, 9H), 0.92 (s, 3H), 0.95 (s, 9H), 1.10 (s, 3H), 1.25-1.76 (m, 4H), 1.93-2.27 (m, 3H), 2.51 (s, 1H), 3.10-3.15 (m, 1H), 3.52 (dd, *J*= 11, 3 Hz, 1H), 4.04-4.28 (m, 4H), 5.94 (d, *J*= 5.7 Hz, 1H); $^{13}C$ NMR δ -5.4, -5.3, -4.1, -4.0, 18.1, 18.2, 20.9, 23.3, 25.8, 25.9, 25.9, 26.1, 26.5, 30.3, 31.9, 33.2, 39.4, 45.6, 48.5,

50.0, 62.6, 66.7, 80.7, 121.1, 126.7, 135.8; HRMS (ESI) calcd for (M+Na) $C_{27}H_{51}NO_3Si_2$ 516.3300, found 516.3290.

**10-(*tert*-Butyl-dimethyl-silanyloxy)-4-(*tert*-butyl-dimethyl-silanyloxymethyl)-7,7-dimethyl-3,3a,6,6a,7,8,9,10-octahydro-2-oxa-cyclopenta[*d*]naphthalen-1-ylideneamine (34).** Solid NaOH (4 mg, 0.1 mmol), water (18 μL, 1 mmol) and the alcohol **30** (5 mg, 0.01 mmol) were added to a room temperature solution (0.5 mL) of butyl-methyl imidazolium chloride. After 2 h the reaction mixture was diluted with water (3 mL), extracted with ethyl acetate and the organic extract was then washed sequentially with aqueous HCl (1 M) and brine, and then dried ($Na_2SO_4$). Concentration and purification by radial chromatography (1:9 EtOAc /hexanes) afforded 2.5 mg (50 %) of recovered **30** and 2.5 mg (50 %) of the iminolactone **34** as a colorless oil: IR (film) 1678 $cm^{-1}$; $^1H$ NMR δ 0.06 (s, 6H), 0.09 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9 H), 0.90 (s, 9H), 0.91 (s, 3H), 1.26 (s, 3H), 1.30-2.52 (m, 8H), 2.92- 2.93 (m, 1H), 3.67-3.72 (m, 1H), 3.89 (d, *J*= 7.8 Hz, 1H), 4.13 (ABq, Δν = 53 Hz, *J*= 13 Hz, 2H), 4.46 (t, *J*= 7.4 Hz, 1H), 5.90 (d, *J*= 4.5 Hz, 1H); HRMS (ESI) calcd for (M + Na) $C_{27}H_{51}NO_3Si_2$ 516.3300, found 516.3328.

**2-(*tert*-Butyl-dimethyl-silanyloxy)-6-(4-iodo-butyl)-cyclohex-1-enecarbonitrile (37).** Using the same protocol as for the synthesis of **14,** an acetone solution (4.5 mL) of NaI (1.2 g, 8.0 mmol) and the chloride[128] (0.5 g, 1.6 mmol) afforded, after radial chromatography (1:19 EtOAc/hexanes), 0.68 g (60 %) of **37** as colorless oil: IR (film), 2208, 1634 $cm^{-1}$; $^1H$ NMR δ 0.49 (s, 6H), 1.23 (s, 9H), 1.52-2.21 (m, 10H), 2.39 (br t, *J*=5 Hz, 2H), 2.47-2.54 (m, 1H), 3.45 (td, *J*= 7, 2 Hz, 2H); $^{13}C$ NMR, δ= -2.6, 7.9, 19.1, 21.7, 26.7, 28.2, 28.9, 31.2, 34.7, 34.9, 36.5, 97.3, 118.0, 164.9; GC/MS m/z 447 (M+H); HRMS (ESI) calcd for (M+Na) $C_{19}H_{34}INOS$: 470.1347, found 470.1351.

**4-Hydroxy-1,1-dimethyl-5-oxo-octahydro-naphthalene-4a-carbonitrile (38)**. Using the same protocol as for the synthesis of **3,** a DMSO solution (3 mL) of the iodide **37** (34 mg, 81 μmol), and *i*-$Pr_2NEt$ (0.07 mL, 0.41 mmol) afforded, after radial chromatography (2:3 EtOAc/hexanes), 15 mg (94 %) of **38** as a colorless oil: IR (film), 2238, 1719 $cm^{-1}$;

$^1$H NMR δ 1.25-1.40 (m, 2H), 1.56-2.02 (m, 7H), 2.14-2.19 (m, 1H), 2.48 (d, *J*= 13.5 Hz, 1H), 2.93 (ddd, *J*= 27, 14, 7 Hz, 2H), 3.28-3.29 (d, *J*= 2.9 Hz, 1H), 3.93-3.97 (dt, *J*=11.5, 2.9 Hz, 1H); $^{13}$C NMR 22.8, 26.3, 28.5, 29.1, 29.6, 39.0, 46.5, 60.8, 69.9, 116.5, 205.7; GC/MS m/z 194 (M+H).

**2-(*tert*-Butyl-dimethyl-silanyloxy)-6-(4-iodo-butyl)-cyclohept-1-enecarbonitrile (40).** A THF solution (4 mL) of 4-chlorobutylmagnesium bromide[158] (0.17 mL, 1.47 mmol) was added to a THF solution (2 mL) of the ketonitrile **39**[125] (57 mg, 0.42 mmol) at –78 °C. After 30 min solid TBSCl (95 mg, 0.63 mmol) was added and the solution was allowed to warm to room temperature overnight. The reaction was then poured into a saturated, aqueous, solution of $NH_4Cl$, the organic layer was extracted (EtOAc) and washed with brine and dried ($Na_2SO_4$). Evaporation of the organic extracts gave after radial chromatography (2:3 EtOAc/hexanes), 16 mg (11 %) of **2-(*tert*-Butyl-dimethyl-silanyloxy)-6-(4-chloro-butyl)-cyclohept-1-enecarbonitrile (i)** as an oil: IR (film) 2203, 1615 cm$^{-1}$; $^1$H NMR δ 0.54 (s, 6H), 1.28 (s, 9H), 1.67-2.10 (m, 9h), 2.16-2.27 (m, 3H), 2.52-2.60 (m, 2H), 2.78 (ddd, *J*= 15, 10, 2 Hz, 1H), 3.80 (t, *J*= 6.6 Hz, 2H); $^{13}$C NMR δ -2.5, 19.2, 25.7, 26.5, 26.8, 30.4, 33.7, 34.1, 35.1, 36.8, 38.9, 45.8, 100.7, 118.3, 170.0, GC/MS (m/z) 342 (M+H). Using the same protocol as for the synthesis of **14**, an acetone solution (4.5 mL) of chloride **i** (29 mg, 85 μmol) and NaI (63 mg, 0.43 mmol) afforded, after radial chromatography (1:19 EtOAc/hexanes), 28 mg (77 %) of **40** as a colorless oil: IR (film) 2203, 1614 cm$^{-1}$; $^1$H NMR, 0.53 (s, 6H), 1.27 (s, 9H), 1.68-2.26 (m, 14H), 2.78 (ddd, *J*= 15, 10, 2 Hz, 1H), 3.48 (t, *J*= 6.9 Hz, 2H); $^{13}$C NMR δ -2.5, -2.5, 7.8, 19.2, 25.7, 26.8, 30.1, 30.4, 33.7, 34.7, 35.0, 36.8, 38.8, 100.7, 118.3, 170.0.

**Cyclohept-1-one-[6,11-*cis*]-cyclobutanecarbonitrile (41).** Using the same protocol as for the synthesis of **3,** a DMSO solution (3 mL) of the iodide **41** (17 mg, 0.039 mmol) and *i*-$Pr_2NEt$ (0.03 mL, 0.20 mmol) afforded after radial chromatography (2:3 EtOAc/ hexanes) 2.1 mg (28 %) of **41** (not spectroscopically pure) and 3.2 mg (42 %) of **42**. $^1$H NMR 1.20-2.03 (m, 15H), 2.62 (ddd, *J*= 10.4, 7.1 Hz, 1H) 2.82-2.91 (m, 1H); $^{13}$C NMR 21.8, 23.1, 25.2, 26.6, 31.1, 32.7, 35.7, 41.2, 43.3, 56.2, 119.3, 205.9; GC/MS (m/z) 192 (M+H).

**2-(*tert*-Butyl-dimethyl-silanyloxy)-6-(4-iodo-1-methylene-butyl)-cyclohex-1-enecarbonitrile (42)** A hexanes solution of n-BuLi (1.8 mL, 2.9 mmol) is added to a –78 °C THF solution (5 mL) of the vinyl iodide **44**[159] (334 mg, 1.45 mmol). After 2 h, a THF solution (3 mL) of $MgBr_2$ (534 mg, 2.9 mmol) is added and the mixture is stirred for 20 min. Neat ketonitrile **6** (50 mg, 0.41 mmol) was added followed after 30 min by solid TBSCl (94 mg, 0.62 mmol) and the solution was then allowed to warm to room temperature overnight. The reaction was then poured into a saturated, aqueous, solution of $NH_4Cl$, the aqueous phase was extracted (EtOAc) and the combined extracts were washed with brine and dried ($Na_2SO_4$). Evaporation of the organic extracts gave, after radial chromatography (1:19 EtOAc/hexanes), 52 mg (46 %) of **2-(*tert*-Butyl-dimethyl-silanyloxy)-6-(4-chloro-1-methylene-butyl)-cyclohex-1-enecarbonitrile (ii)** as an oil: IR (film), 2209, 1627 $cm^{-1}$; $^1H$ NMR 0.56 (s, 6H), 1.29 (s, 9H), 1.87-2.11 (m, 4H), 2.21-2.30 (m, 2H), 2.37-2.56 (m, 4H), 3.27 (t, *J*= 5 Hz, 1H), 3.83 (ddd, *J*=12.2, 6, 3 Hz, 2H), 5.16 (s, 1H), 5.31 (d, *J*=1Hz, 1H); $^{13}C$ NMR δ -2.5, 7.9, 19.2, 20.5, 26.8, 28.3, 32.2, 32.4, 43.9, 45.4, 95.4, 114.4, 117.9, 148.9, 165.5; GC/MS m/z 340 (M+H). The chloride **ii** (25 mg, 0.07 mmol) was treated with NaI (220 mg, 1.47 mmol) in acetone (3 mL) using the same protocol as for **14** to afford, after radial chromatography (1:19 EtOAc/hexanes), 23 mg (72 %) of **42** as an oil: IR (film) 2210 $cm^{-1}$; $^1H$ NMR, δ 0.55 (s, 3H), 0.56 (s, 3H), 1.29 (s, 9H), 1.82-2.11 (m, 4H), 2.23-2.56 (m, 6H), 3.24-3.26 (m, 1H) 3.43-3.59 (m, 2H), 5.15 (s, 1H), 5.32 (d, *J*=1Hz, 1H); $^{13}C$ NMR δ -2.5, 7.8, 19.2, 20.5, 26.8, 28.3, 32.2, 32.9, 36.0, 43.9, 95.4, 114.6, 117.9, 148.6, 165.5; GC/MS (m/z) 431 (M).

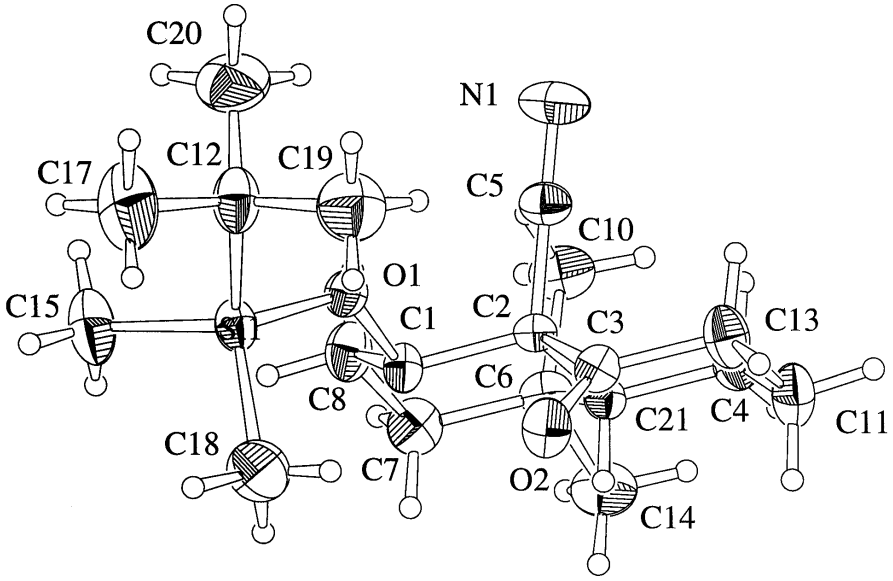
**1-methylene-5-oxo-octahydro-naphthalene-4a-carbonitrile (43)** Cyclization of a DMSO solution (5 mL) of the iodide **42** (100 mg, 0.23 mmol) with *i*-$Pr_2NEt$ (0.2 mL, 1.2 mmol) following the protocol used for **3**, afforded, after radial chromatography (2:3 EtOAc/hexanes), 40 mg (93 %) of **43** as an oil: IR (film) 3076, 2240, 1714 $cm^{-1}$; $^1H$ NMR δ 1.72-2.30 (m, 10H), 2.50-2.55 (m, 2H), 2.87 (dd, *J*= 12, 4 Hz, 1H), 4.92 (d, *J*=8.2 Hz, 2H); $^{13}C$ NMR δ 24.0, 24.5, 26.1, 28.3, 29.7, 36.9, 50.4, 55.7, 112.7, 118.9, 144.3, 203.0; GC/MS (m/z) 190 (M+H).

**1,1-dimethyl-5-oxo-octahydro-naphthalene-4a-carbonitrile (47).** A toluene solution (3 mL) of trimethylaluminum (1 mL, 2 mmol) was added to a suspension of $NH_4Cl$ (107 mg, 2 mmol) in toluene (4 mL) at 0 °C. The mixture was stirred at room temperature for 2 h to afford a 0.34 M solution of the requisite aluminum amide reagent and then neat *cis*-decalin **19** (20 mg, 0.1 mmol) was added and heated to reflux for 20 h. After cooling to room temperature, the mixture was filtered through a pad of silica gel to afford 11 mg (59 %) of **47** that was spectroscopically identical to material prepared previously.[128]

## 5.0 Appendix

## 5.1 Appendix 1. Crystallographic Data for 4-(*tert*-Butyl-dimethyl-silanyloxy)-1,1-dimethyl-5-oxo-octahydro-naphthalene-4a-carbonitrile

**Figure 1. ORTEP of 3b**



**CIF Data for 4-(*tert*-Butyl-dimethyl-silanyloxy)-1,1-dimethyl-5-oxo-octahydro-naphthalene-4a-carbonitrile**

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 C(1) C(2) 1.542(5) . . yes
 C(1) C(8) 1.513(6) . . yes
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 C(2) C(5) 1.469(6) . . yes
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 C(3) C(13) 1.493(6) . . yes
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 C(4) C(21) 1.527(5) . . yes
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 C(4) H(3) 0.95 . . no
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 C(6) C(10) 1.537(6) . . yes
 C(6) C(14) 1.533(6) . . yes
 C(6) C(21) 1.548(5) . . yes
 C(7) C(8) 1.515(6) . . yes
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 C(7) H(5) 0.95 . . no
 C(8) H(6) 0.95 . . no
 C(8) H(7) 0.95 . . no
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 C(10) H(13) 0.95 . . no
 C(10) H(14) 0.95 . . no
 C(11) C(13) 1.521(7) . . yes
 C(11) H(8) 0.96 . . no
 C(11) H(9) 0.95 . . no
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 C(12) C(19) 1.549(8) . . yes
 C(12) C(20) 1.526(7) . . yes
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 C(14) H(17) 0.95 . . no
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 O(1) C(1)  C(8) 111.1(3) . . . yes
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 C(7) C(6)  C(10) 111.8(4) . . . yes
 C(7) C(6)  C(14) 107.6(4) . . . yes
 C(7) C(6)  C(21) 108.3(3) . . . yes
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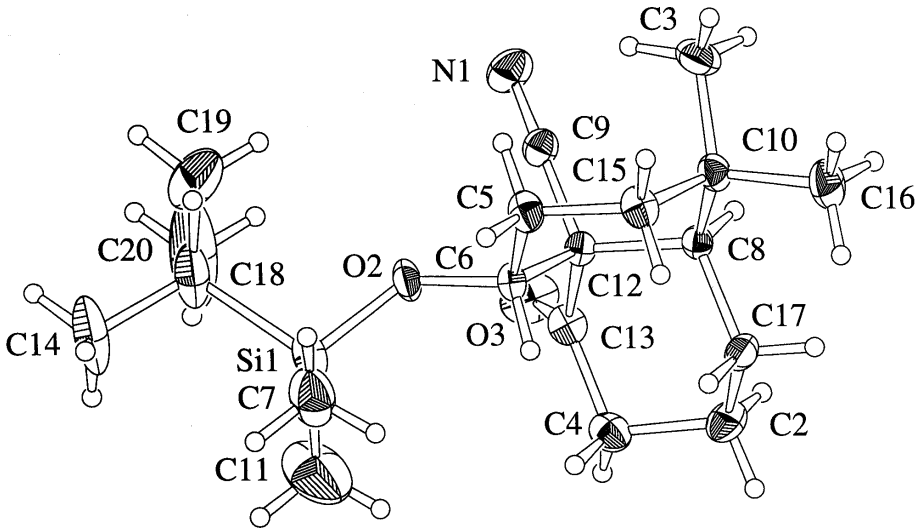
```

## 5.2 Appendix II. Crystallographic Data for 4-(*tert*-Butyl-dimethyl-silanyloxy)-1,1-dimethyl-5-oxo-octahydro-naphthalene-4a-carbonitrile

**Figure 2. ORTEP of 10b**



**CIF Data for 4-(*tert*-Butyl-dimethyl-silanyloxy)-1,1-dimethyl-5-oxo-octahydro-naphthalene-4a-carbonitrile**

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Molecular Structure Corporation. (1992-1997). teXsan.
Single Crystal Structure Analysis Software. Version 1.7.
MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

North, A.C.T., Phillips, D. C. & Mathews, F. S. (1968).
Acta Cryst. A24, 351-359.
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_cell_angle_gamma                      90
_cell_volume                           2095.6(9)
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  '   -x,   -y,   -z'
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\y scans (North,Phillips & Matthews, 1968)
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(up to 4 scans to achieve I/\s(I) > 10).
Stationary background counts were recorded at each end of the
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  C  0    80 0.003 0.002
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(1992, Vol. C, Tables 4.2.6.8 and 6.1.1.1)
;
  H  0   132 0.000 0.000
;International Tables for Crystallography
(1992, Vol. C, Table 6.1.1.2)
;
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  N  0     4 0.006 0.003
;International Tables for Crystallography
(1992, Vol. C, Tables 4.2.6.8 and 6.1.1.1)
;
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;International Tables for Crystallography
(1992, Vol. C, Tables 4.2.6.8 and 6.1.1.1)
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  Si 0     4 0.082 0.070
;International Tables for Crystallography
(1992, Vol. C, Tables 4.2.6.8 and 6.1.1.1)
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_atom_site_adp_type
_atom_site_calc_flag
_atom_site_calc_attached_atom
Si(1) 0.7771(2) 0.0893(2) 0.7959(2) 0.0660(6) 1.000 . Uani d ?
O(2) 0.6454(3) 0.1420(3) 0.7455(3) 0.052(1) 1.000 . Uani d ?
O(3) 0.5256(6) 0.2859(4) 0.8821(3) 0.086(2) 1.000 . Uani d ?
N(1) 0.4700(6) 0.3580(4) 0.6609(4) 0.068(2) 1.000 . Uani d ?
C(2) 0.3417(6) 0.0836(6) 0.8777(5) 0.061(2) 1.000 . Uani d ?
C(3) 0.2496(7) 0.2027(6) 0.5268(4) 0.063(2) 1.000 . Uani d ?
C(4) 0.4749(6) 0.1148(5) 0.9129(4) 0.054(2) 1.000 . Uani d ?
C(5) 0.4865(5) 0.0721(5) 0.6096(4) 0.050(2) 1.000 . Uani d ?
C(6) 0.5286(4) 0.0995(4) 0.7165(4) 0.038(1) 1.000 . Uani d ?
C(7) 0.7818(8) -0.0437(7) 0.7424(7) 0.098(3) 1.000 . Uani d ?
C(8) 0.3127(5) 0.1419(4) 0.7039(4) 0.036(1) 1.000 . Uani d ?
C(9) 0.4595(5) 0.2806(4) 0.6948(4) 0.044(2) 1.000 . Uani d ?
C(10) 0.2678(5) 0.1089(4) 0.5940(4) 0.043(1) 1.000 . Uani d ?
C(11) 0.810(1) 0.079(1) 0.9299(7) 0.169(6) 1.000 . Uani d ?
C(12) 0.4457(5) 0.1809(4) 0.7400(4) 0.034(1) 1.000 . Uani d ?
C(13) 0.4886(6) 0.2022(5) 0.8498(4) 0.049(2) 1.000 . Uani d ?
C(14) 1.0123(8) 0.1438(9) 0.8090(9) 0.128(4) 1.000 . Uani d ?
C(15) 0.3576(6) 0.0332(5) 0.5758(4) 0.049(2) 1.000 . Uani d ?
C(16) 0.1453(6) 0.0546(5) 0.5677(5) 0.065(2) 1.000 . Uani d ?
C(17) 0.2990(5) 0.0555(4) 0.7723(4) 0.049(2) 1.000 . Uani d ?
C(18) 0.8816(7) 0.1804(7) 0.7665(8) 0.091(3) 1.000 . Uani d ?
C(19) 0.844(1) 0.188(1) 0.6547(9) 0.180(7) 1.000 . Uani d ?
C(20) 0.878(1) 0.2831(9) 0.819(1) 0.218(7) 1.000 . Uani d ?
H(1) 0.3317 0.0255 0.9144 0.073 1.000 . Uiso c ?
H(2) 0.2958 0.1404 0.8874 0.073 1.000 . Uiso c ?
H(3) 0.3233 0.2386 0.5402 0.076 1.000 . Uiso c ?
H(4) 0.2222 0.1799 0.4610 0.076 1.000 . Uiso c ?
H(5) 0.1919 0.2478 0.5374 0.076 1.000 . Uiso c ?
H(6) 0.4990 0.1368 0.9789 0.065 1.000 . Uiso c ?
H(7) 0.5224 0.0573 0.9074 0.065 1.000 . Uiso c ?
H(8) 0.4911 0.1320 0.5731 0.059 1.000 . Uiso c ?
H(9) 0.5366 0.0191 0.5991 0.059 1.000 . Uiso c ?
```

```
H(10) 0.5298 0.0382 0.7532 0.046 1.000 . Uiso c ?
H(11) 0.7228 -0.0868 0.7536 0.118 1.000 . Uiso c ?
H(12) 0.7663 -0.0374 0.6745 0.118 1.000 . Uiso c ?
H(13) 0.8587 -0.0734 0.7726 0.118 1.000 . Uiso c ?
H(14) 0.2643 0.1985 0.7099 0.043 1.000 . Uiso c ?
H(15) 0.7513 0.0368 0.9422 0.203 1.000 . Uiso c ?
H(16) 0.8869 0.0479 0.9590 0.203 1.000 . Uiso c ?
H(17) 0.8099 0.1461 0.9564 0.203 1.000 . Uiso c ?
H(18) 1.0333 0.1340 0.8769 0.154 1.000 . Uiso c ?
H(19) 1.0209 0.0800 0.7790 0.154 1.000 . Uiso c ?
H(20) 1.0631 0.1947 0.7961 0.154 1.000 . Uiso c ?
H(21) 0.3334 0.0201 0.5078 0.059 1.000 . Uiso c ?
H(22) 0.3554 -0.0299 0.6091 0.059 1.000 . Uiso c ?
H(23) 0.0885 0.1014 0.5775 0.078 1.000 . Uiso c ?
H(24) 0.1197 0.0337 0.5013 0.078 1.000 . Uiso c ?
H(25) 0.1522 -0.0048 0.6079 0.078 1.000 . Uiso c ?
H(26) 0.3431 -0.0033 0.7641 0.059 1.000 . Uiso c ?
H(27) 0.2165 0.0380 0.7535 0.059 1.000 . Uiso c ?
H(28) 0.7631 0.2109 0.6292 0.216 1.000 . Uiso c ?
H(29) 0.8941 0.2364 0.6381 0.216 1.000 . Uiso c ?
H(30) 0.8510 0.1218 0.6289 0.216 1.000 . Uiso c ?
H(31) 0.9016 0.2717 0.8869 0.261 1.000 . Uiso c ?
H(32) 0.9306 0.3320 0.8055 0.261 1.000 . Uiso c ?
H(33) 0.7985 0.3104 0.7960 0.261 1.000 . Uiso c ?

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_atom_site_aniso_U_33
_atom_site_aniso_U_12
_atom_site_aniso_U_13
_atom_site_aniso_U_23
 Si(1)  0.0377(8)   0.081(1)    0.077(1)    0.008(1)    0.0167(9)   -
0.005(1)
 O(2)   0.025(2)    0.059(3)    0.068(3)    -0.003(2)   0.007(2)
0.002(2)
 O(3)   0.122(5)    0.063(3)    0.067(3)    -0.030(3)   0.024(3)    -
0.025(2)
 N(1)   0.081(4)    0.041(3)    0.088(4)    -0.013(3)   0.035(4)
0.003(3)
 C(2)   0.065(4)    0.074(5)    0.056(3)    0.000(4)    0.037(3)
0.007(4)
 C(3)   0.060(4)    0.067(4)    0.050(3)    0.005(4)    0.001(3)
0.011(3)
 C(4)   0.057(4)    0.067(4)    0.037(3)    0.009(3)    0.014(3)    -
0.003(3)
 C(5)   0.043(3)    0.067(4)    0.041(3)    0.003(3)    0.017(2)    -
0.009(3)
 C(6)   0.028(2)    0.042(3)    0.045(3)    -0.003(2)   0.011(2)    -
0.008(2)
 C(7)   0.069(5)    0.070(5)    0.153(8)    0.012(5)    0.035(6)
0.002(5)
 C(8)   0.032(2)    0.029(2)    0.047(3)    0.002(2)    0.014(2)
0.001(2)
 C(9)   0.045(3)    0.040(3)    0.048(3)    -0.004(3)   0.018(3)    -
0.002(3)
```

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 C(10)  0.035(3)    0.041(3)    0.048(3)    -0.003(2)   0.008(2)    -
0.002(2)
 C(11)  0.14(1)     0.30(2)     0.065(5)    0.07(1)     0.038(7)
0.025(8)
 C(12)  0.035(3)    0.029(2)    0.041(3)    -0.001(2)   0.015(2)    -
0.005(2)
 C(13)  0.052(3)    0.047(3)    0.048(3)    0.000(3)    0.016(3)    -
0.010(3)
 C(14)  0.040(4)    0.14(1)     0.20(1)     -0.006(6)   0.028(6)    -
0.043(9)
 C(15)  0.046(3)    0.055(4)    0.044(3)    0.000(3)    0.011(3)    -
0.014(3)
 C(16)  0.042(3)    0.065(4)    0.078(5)    -0.012(3)   0.009(3)    -
0.011(4)
 C(17)  0.046(3)    0.045(3)    0.064(4)    0.001(3)    0.029(3)
0.010(3)
 C(18)  0.044(4)    0.073(5)    0.157(8)    -0.005(4)   0.036(5)    -
0.023(6)
 C(19)  0.13(1)     0.28(2)     0.15(1)     -0.02(1)    0.074(9)
0.08(1)
 C(20)  0.092(9)    0.090(8)    0.48(3)     -0.028(7)   0.10(1)     -
0.12(1)
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_refine_ls_goodness_of_fit_all         ?
_refine_ls_goodness_of_fit_ref         2.940
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_refine_diff_density_max               0.66
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 Si(1) O(2) 1.632(4) . . yes
 Si(1) C(7) 1.889(9) . . yes
 Si(1) C(11) 1.863(9) . . yes
 Si(1) C(18) 1.858(9) . . yes
 O(2) C(6) 1.416(6) . . yes
 O(3) C(13) 1.198(7) . . yes
 N(1) C(9) 1.136(7) . . yes
 C(2) C(4) 1.541(9) . . yes
 C(2) C(17) 1.493(8) . . yes
 C(2) H(1) 0.95 . . no
 C(2) H(2) 0.95 . . no
 C(3) C(10) 1.524(8) . . yes
 C(3) H(3) 0.95 . . no
 C(3) H(4) 0.95 . . no
 C(3) H(5) 0.95 . . no
 C(4) C(13) 1.496(9) . . yes
 C(4) H(6) 0.95 . . no
 C(4) H(7) 0.95 . . no
 C(5) C(6) 1.509(7) . . yes
 C(5) C(15) 1.524(8) . . yes
 C(5) H(8) 0.95 . . no
 C(5) H(9) 0.95 . . no
 C(6) C(12) 1.552(7) . . yes
 C(6) H(10) 0.95 . . no
 C(7) H(11) 0.95 . . no
 C(7) H(12) 0.95 . . no
 C(7) H(13) 0.95 . . no
 C(8) C(10) 1.567(7) . . yes
 C(8) C(12) 1.568(7) . . yes
 C(8) C(17) 1.538(7) . . yes
 C(8) H(14) 0.95 . . no
 C(9) C(12) 1.477(7) . . yes
 C(10) C(15) 1.532(8) . . yes
 C(10) C(16) 1.539(8) . . yes
 C(11) H(15) 0.95 . . no
 C(11) H(16) 0.95 . . no
 C(11) H(17) 0.94 . . no
 C(12) C(13) 1.533(7) . . yes
 C(14) C(18) 1.54(1) . . yes
 C(14) H(18) 0.95 . . no
 C(14) H(19) 0.95 . . no
 C(14) H(20) 0.95 . . no
 C(15) H(21) 0.95 . . no
 C(15) H(22) 0.95 . . no
 C(16) H(23) 0.95 . . no
 C(16) H(24) 0.95 . . no
 C(16) H(25) 0.95 . . no
 C(17) H(26) 0.95 . . no
 C(17) H(27) 0.95 . . no
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 C(18) C(19) 1.54(1) . . yes
 C(18) C(20) 1.54(1) . . yes
 C(19) H(28) 0.95 . . no
 C(19) H(29) 0.95 . . no
 C(19) H(30) 0.95 . . no
 C(20) H(31) 0.94 . . no
 C(20) H(32) 0.95 . . no
 C(20) H(33) 0.95 . . no
#------------------------------------------------------------------------
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 O(2) Si(1)  C(7) 110.3(3) . . . yes
 O(2) Si(1)  C(11) 109.4(4) . . . yes
 O(2) Si(1)  C(18) 104.3(3) . . . yes
 C(7) Si(1)  C(11) 110.2(6) . . . yes
 C(7) Si(1)  C(18) 111.1(4) . . . yes
 C(11) Si(1)  C(18) 111.3(6) . . . yes
 Si(1) O(2)  C(6) 131.8(4) . . . yes
 C(4) C(2)  C(17) 111.1(5) . . . yes
 C(4) C(2)  H(1) 109.0 . . . no
 C(4) C(2)  H(2) 109.0 . . . no
 C(17) C(2)  H(1) 109.0 . . . no
 C(17) C(2)  H(2) 109.1 . . . no
 H(1) C(2)  H(2) 109.5 . . . no
 C(10) C(3)  H(3) 109.4 . . . no
 C(10) C(3)  H(4) 109.4 . . . no
 C(10) C(3)  H(5) 109.4 . . . no
 H(3) C(3)  H(4) 109.5 . . . no
 H(3) C(3)  H(5) 109.6 . . . no
 H(4) C(3)  H(5) 109.5 . . . no
 C(2) C(4)  C(13) 107.6(5) . . . yes
 C(2) C(4)  H(6) 109.9 . . . no
 C(2) C(4)  H(7) 109.9 . . . no
 C(13) C(4)  H(6) 110.0 . . . no
 C(13) C(4)  H(7) 110.0 . . . no
 H(6) C(4)  H(7) 109.5 . . . no
 C(6) C(5)  C(15) 110.9(5) . . . yes
 C(6) C(5)  H(8) 109.2 . . . no
 C(6) C(5)  H(9) 109.1 . . . no
 C(15) C(5)  H(8) 109.1 . . . no
 C(15) C(5)  H(9) 109.1 . . . no
 H(8) C(5)  H(9) 109.5 . . . no
 O(2) C(6)  C(5) 110.4(5) . . . yes
 O(2) C(6)  C(12) 107.6(4) . . . yes
 O(2) C(6)  H(10) 108.9 . . . no
 C(5) C(6)  C(12) 111.8(4) . . . yes
 C(5) C(6)  H(10) 109.0 . . . no
 C(12) C(6)  H(10) 109.0 . . . no
 Si(1) C(7)  H(11) 109.3 . . . no
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Si(1) C(7)  H(12) 109.4 . . . no
Si(1) C(7)  H(13) 109.3 . . . no
H(11) C(7)  H(12) 109.6 . . . no
H(11) C(7)  H(13) 109.6 . . . no
H(12) C(7)  H(13) 109.6 . . . no
C(10) C(8)  C(12) 112.7(4) . . . yes
C(10) C(8)  C(17) 113.1(4) . . . yes
C(10) C(8)  H(14) 107.1 . . . no
C(12) C(8)  C(17) 109.2(4) . . . yes
C(12) C(8)  H(14) 107.2 . . . no
C(17) C(8)  H(14) 107.2 . . . no
N(1) C(9)  C(12) 179.2(6) . . . yes
C(3) C(10)  C(8) 111.6(5) . . . yes
C(3) C(10)  C(15) 110.3(5) . . . yes
C(3) C(10)  C(16) 106.4(5) . . . yes
C(8) C(10)  C(15) 109.5(4) . . . yes
C(8) C(10)  C(16) 110.2(5) . . . yes
C(15) C(10)  C(16) 108.8(5) . . . yes
Si(1) C(11)  H(15) 109.2 . . . no
Si(1) C(11)  H(16) 109.2 . . . no
Si(1) C(11)  H(17) 109.8 . . . no
H(15) C(11)  H(16) 108.8 . . . no
H(15) C(11)  H(17) 109.9 . . . no
H(16) C(11)  H(17) 109.8 . . . no
C(6) C(12)  C(8) 110.6(4) . . . yes
C(6) C(12)  C(9) 108.2(4) . . . yes
C(6) C(12)  C(13) 109.9(4) . . . yes
C(8) C(12)  C(9) 112.3(4) . . . yes
C(8) C(12)  C(13) 110.4(5) . . . yes
C(9) C(12)  C(13) 105.3(4) . . . yes
O(3) C(13)  C(4) 122.3(5) . . . yes
O(3) C(13)  C(12) 121.3(6) . . . yes
C(4) C(13)  C(12) 116.2(5) . . . yes
C(18) C(14)  H(18) 109.6 . . . no
C(18) C(14)  H(19) 109.2 . . . no
C(18) C(14)  H(20) 109.3 . . . no
H(18) C(14)  H(19) 109.7 . . . no
H(18) C(14)  H(20) 109.8 . . . no
H(19) C(14)  H(20) 109.3 . . . no
C(5) C(15)  C(10) 114.6(5) . . . yes
C(5) C(15)  H(21) 108.2 . . . no
C(5) C(15)  H(22) 108.2 . . . no
C(10) C(15)  H(21) 108.2 . . . no
C(10) C(15)  H(22) 108.2 . . . no
H(21) C(15)  H(22) 109.4 . . . no
C(10) C(16)  H(23) 109.5 . . . no
C(10) C(16)  H(24) 109.4 . . . no
C(10) C(16)  H(25) 109.5 . . . no
H(23) C(16)  H(24) 109.5 . . . no
H(23) C(16)  H(25) 109.5 . . . no
H(24) C(16)  H(25) 109.5 . . . no
C(2) C(17)  C(8) 114.8(5) . . . yes
C(2) C(17)  H(26) 108.3 . . . no
C(2) C(17)  H(27) 108.2 . . . no
C(8) C(17)  H(26) 108.1 . . . no
C(8) C(17)  H(27) 108.0 . . . no
H(26) C(17)  H(27) 109.5 . . . no
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```
 Si(1) C(18)  C(14) 112.1(7) . . . yes
 Si(1) C(18)  C(19) 107.8(7) . . . yes
 Si(1) C(18)  C(20) 107.0(8) . . . yes
 C(14) C(18)  C(19) 110(1) . . . yes
 C(14) C(18)  C(20) 104.8(9) . . . yes
 C(19) C(18)  C(20) 115(1) . . . yes
 C(18) C(19)  H(28) 109.2 . . . no
 C(18) C(19)  H(29) 109.2 . . . no
 C(18) C(19)  H(30) 109.2 . . . no
 H(28) C(19)  H(29) 109.8 . . . no
 H(28) C(19)  H(30) 109.8 . . . no
 H(29) C(19)  H(30) 109.7 . . . no
 C(18) C(20)  H(31) 110.0 . . . no
 C(18) C(20)  H(32) 109.3 . . . no
 C(18) C(20)  H(33) 109.2 . . . no
 H(31) C(20)  H(32) 109.8 . . . no
 H(31) C(20)  H(33) 109.7 . . . no
 H(32) C(20)  H(33) 108.8 . . . no
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 O(3)      C(15)     3.440(8)   . 2_656 no
 N(1)      C(6)      3.582(8)   . 2_656 no
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 N(1) C(9) C(12) C(8) . . . . 93.7(5) no
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